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HEMOPHILIA IN THE NEGRO.*

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It is questionable whether true hemophilia exists in the negro race. In 1911, Bulloch and Fildes[1] presented their exhaustive monograph in which they announced the ability to trace all but six of the papers on this hemorrhagic diathesis existing in the literature of the world. Preceding this paper there were but 3 reports of alleged hemophilia in the negro. Since 1911 there have appeared no further accounts of its occurrence in that race.

The 3 existing accounts of hemophilia in the negro appear in abstract in the following paragraphs along with a brief discussion as to their merits as instances of this disease.

In 1874, there appeared in the "Clinic" of Cincinnati the presentation of the first report. Dr. Hadlock[2] described bleeding in a mulatto boy aged 7 years. The bleeding occurred from the gums at the base of a loose decayed tooth. Removal of the tooth caused an increase rather than the expected cessation of the hemorrhage. Persulphate of iron pledgets were applied to the bleeding socket with little effect. Silver nitrate locally and astringents internally were likewise of very temporary value. Following this a series of astringents and styptics was used to no avail, for the boy died from exsanguination 48 hours later. Dr. Hadlock mentioned no laboratory studies. He stated that there had been many deaths in this boy's family due to hemorrhage occurring from slight wounds. It was

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more specifically noted that an uncle died as a result of hemorrhage from a cut with a scythe, and that the father of the boy bled to death following a briar scratch. Two brothers died of tuberculosis. There was no mention of a bleeding tendency among females in this family. This appears to be an example of true hemophilia but the presence of white ancestry in the mulatto excludes this case from a consideration of hemophilia in the negro.

The next instance of the disease in a negro was reported by Dr. W. R. Steiner[3] in 1900. His patient was a negro girl aged 14, who was admitted to the hospital with hemorrhage from the nose and mouth, and headache. Her past medical history stated that she had bled easily from the slightest scratches since early childhood but that the amount of blood lost has been slight in every instance. There had been no epistaxis previous to the present illness. The present illness began $2\frac{1}{2}$ months before admission when the patient lost about a cupful of blood due to a spontaneous nosebleed. Following this she felt weak and drowsy until her entrance into the hospital. Five days and 2 days before the admission epistaxis recurred.

There were herpetic lesions on the lower lip and over the clavicular areas. Three days after admission the gums were swollen and bled easily and purpuric spots appeared on the arms and legs.

The family history states that a brother had had a painful, swollen ankle joint following acute urethritis. The diagnosis was gonorrheal arthritis but Dr. Steiner suggests a possible hemarthrosis due to hemophilia. Six other brothers suffered occasionally from epistaxis and bled considerably from slight cuts and bruises. One died at the age of 34 of hemorrhage from the nose and mouth. There were 3 sisters who were not disturbed by a bleeding tendency. The mother bled from the nose at intervals until she was 16 when the bleeding tendency ceased. The grandmother occasionally bled from the nose and died at the age of 60 years from asthma, dropsy, Bright's disease and heart disease. The great-grandmother was a bleeder from childhood but, despite semi-annual cupping and leeching, she survived to die of old age.

The coagulation time on this patient was 3 to 4 minutes and the platelet count 212,000 per c.mm. No other laboratory studies were mentioned.

This is an instance of alleged hemophilia in a negress. Hemophilia probably does not occur in this sex despite numerous reports. Bulloch and Fildes found no typical example of hemophilia in the female in over 900 cases of the disease. Muir[4] traced the genealogy of a hemophilic family through 7 generations including over 600 members and concluded that there was no greater tendency to bleed among the women of this family than in an equal number of women having no hemophilic connections. During the period from 1922 to 1936 there have been 12 patients with alleged hemophilia admitted to this hospital. All were in white males. But 5 of the 12

case histories bear careful scrutiny as to the accuracy of the diagnosis.

Steiner's case emphasizes the fact that when viewed over a period of several generations, some members of a given family are apt to display instances of hemorrhage. The family history in his case can scarcely be construed as that of hemorrhagic diathesis. The history, the physical findings of purpuric spots and hemorrhage from the gums, and a normal coagulation time seem to place this patient in the category of purpura, possibly of the familial or anaphylactoid type.

The third instance of hemophilia in the negro was that of a report of 2 cases by Dr. Louis Buck,[5] of Portland, Oregon. His first case occurred in a negro male 30 years of age, who came to Dr. Buck suffering from spontaneous epistaxis. The nasal passages were packed with gauze, a posterior nasal pack was placed and calcium chloride 10 grains administered every 3 hours. The bleeding ceased and there was no further trouble. No laboratory findings, family history or past history were given.

His second case was that of a negress 24 years of age. She likewise presented severe epistaxis which was treated by gauze nasal packs. These packs were left in place for 7 days and the hemorrhage thereby controlled. No further episodes occurred. Here also no laboratory findings, family history or past history were noted. These 2 case reports of severe epistaxis warrant little discussion as instances of true hemophilia. It seems logical to suppose that there was little in the past history to suggest bleeding episodes and hemophilics seldom reach the third decade of life without some serious hemorrhagic manifestations. Furthermore one of these patients was a female.

Thus there is apparently no instance on record of hemophilia in the full blooded negro. The following example of hemophilia is therefore thought to be of sufficient interest to warrant its report.

Clinical History. The subsequent remarks concern a colored boy, J. B., aged 10 years.

His family history states that he has 4 siblings: a sister aged 6 years, who is living and well, another sister who died at the age of 1 year of diabetes, and 2 brothers, 13 and 6, who are living and well. Both brothers have nosebleeds on the average of once a week. Their bleeding times (Ivy method) were $4\frac{1}{2}$ and $2\frac{1}{2}$ minutes respectively. Coagulation time (capillary tube) 3 and $3\frac{1}{2}$ minutes; platelets (Olaf's method) 238,000 and 480,000 (May, 1936). The father is living and well and has no tendency to bleed. The mother is living and well, and in her family there are 9 brothers, all of whom are in good health and in which there is no history of bleeding except in the youngest, now 25, who has had frequent nosebleeds since childhood but no tendency to hemorrhage from cuts and no swollen joints. The patient's grandfather on the maternal side had frequent nosebleeds during the last few years of his life, but died of hypertension at the age of 76. There were no known bleeders among the mother's uncles. The mother of the patient has 6 sisters among the families of whom there is a total of 18 sons, all of whom are living and well and none of whom display a hemorrhagic tendency.

The mother, when questioned concerning interbreeding with the whites, stated that her grandmother (paternal) was a very black negress; her father and mother were likewise very black. Brothers and sisters of the mother are all dark and she knows of no instance of a light colored person in her family. The mother likewise knows many of her husband's family and states that there are first cousins of his who are light and have been "mixed up with the whites" but that these are all the offspring of one uncle and that the light tendency occurs in no other branch. (The information concerning these light negroes furnished in contemptuous tone.)

The hemophilic boy and his 2 brothers are the blackest of negroes and their appearance is certainly against the impression that they may possess white ancestors.

The past medical history states that at birth there was no unusual bleeding from the cord. At the age of 3 or 4, the child began to bleed from the nose once or twice a week. At the age of 6 or 7, it was first noticed that cuts would bleed intermittently for 3 or 4 days. During the 3 or 4 years previous to admission, the family has noted frequent swellings of the ankles, knees and wrists occurring after hard play, usually connected with a fall. These swellings would last a week or more. There was never any hematuria, melena or hematemesis. The boy has never before been hospitalized. He has apparently been normal as to his activities. He had influenza at the age of 1 year, typhoid fever and chicken pox both at 2 years of age. He was a full term baby, born by spontaneous delivery. He sat up at a later date than normal and did not walk for over 1 year. He talked at the "appropriate time." He received no orange juice until the age of 18 months.

He was admitted to this hospital for the first time on May 28, 1935. At this time his chief complaint was bleeding from the gums. He had been bleeding for about 1 week and on the day of admission the bleeding became more profuse and the family became alarmed. The father stated that his diet had been replete with vegetables and that he had had no pain in his arms or legs since the onset of the present bleeding episode. He had been receiving fruit on an average of once a week.

Physical examination revealed an apprehensive, somewhat listless, but coöperative young colored boy, moderately well nourished. He showed marked pallor of the mucous membranes and the conjunctivæ. The eye grounds showed no hemorrhage. The gums, lips and oral mucous membranes were pale; the gums were firm and there was blood oozing from them along all the upper left teeth. The incisors were notched but not of the Hutchinson type. The pharynx was injected and the tonsils were present. The glands showed a generalized enlargement of those of the neck, groin, axillæ and the epitrochlears. The spleen was not palpable. The neck was normal except for the adenitis. The lungs were normal. The heart was rapid (102 per minute). The rhythm was regular; there was no enlargement. There was a systolic murmur heard over the entire precordium. The abdomen was not tender; no palpable organs with the exception of the liver edge which could be felt at the costal margin on deep inspiration. The genitalia were normal. The extremities showed pallor of the nail beds. There was no pain over the long bones and the reflexes were normal throughout.

On June 5, 1935, a tooth was extracted and the patient bled for 3 days, after which he felt well. On June 14, he fell and cut his right little finger. It was noted that he bled readily and soaked the dressings.

Laboratory studies on May 29, 1935, showed the hemoglobin to be 48%; R.B.C. 2,970,000; W.B.C. 7100 of which 55% were neutrophils, 5% eosinophils, 1% basophils and 39% lymphocytes. The blood sugar was 57 mg. %; the blood calcium was 9.8 mg. % and the blood phosphorus 5.2 mg. %. The Wassermann and Kahn tests were both negative. On

June 3, roentgenograms of the knee regions were negative for evidence of scurvy. The boy was discharged on June 14 without definite diagnosis as to the cause of the bleeding.

On July 15, 1935, he returned to the Out Patient Department Dental Clinic where he was not recognized and where the family denied a history of bleeding. Consequently another tooth was extracted. On July 16, he was readmitted to the hospital because of bleeding from the tooth socket. Attempt to control the hemorrhage by thromboplastin and packing locally and 10 cc. of thromboplastin intravenously was unsuccessful. He was still oozing on July 17 when his hemoglobin was 48% and his R.B.C. 2,710,000. His pulse was 130. On July 18 the bleeding continued and an indirect transfusion of 200 cc. of citrated blood was given. One hour after the transfusion there was a chill and a rise in temperature to 104° F. The hemorrhage ceased. Subsequently there occurred a minute amount of hemorrhage for 1 day.

On July 23, he was transferred to the medical service. It was here noted that the mucous membranes, conjunctivæ and nail beds were almost white. The pulse rate was 116, the spleen not palpable. On this day the R.B.C. were 2,300,000 and the platelets 320,000 per c.mm. On August 7, the patient was up and about the ward and a note was made to the effect that he was a disciplinary problem. Four days later it was noticed that there was limping due to considerable swelling of the left knee. This knee was not hot or tender but was painful on motion. On questioning the patient, he revealed that while playing in a wheelchair the night before, he had bumped the knee against one of the arms of the chair. The intern made a diagnosis of hemophilia with hemarthrosis. The bleeding and coagulation times were taken and found to be 2½ minutes and 1 hour and 45 minutes plus, respectively.

Five days later swelling in the knee was subsiding. The patient had some fever which was unexplainable other than by absorption of the products of the clot in the knee joint. On August 21, the knee was flexed to about 120 degrees and there was marked distention of the joint space with little motion possible. The joint was tapped and 20 cc. of bloody fluid obtained. Three days later on repeated tapping, 100 cc. of dark fluid was removed. During this time the patient was receiving daily intramuscular injections of from 10 to 20 cc. of whole blood. On September 1, oozing began from the point at which the needle was introduced for the knee tap 9 days previously. On September 4, he was still bleeding and 10 cc. of fresh rabbit serum was injected intramuscularly. The blood pressure was 108/60, the pulse 180, the coagulation time 38 minutes. The patient was given a transfusion of 200 cc. of citrated blood. For this transfusion both the mother and father were typed and the Wassermann and Kahn tests on both were negative. The following day the pulse dropped to 130, and the coagulation time was 13 minutes. Two days later he was given a third transfusion of 175 cc. of citrated blood. On September 11, rabbit serum was again given intramuscularly. Bleeding continued intermittently from the tap wound from September 1 to 18, 1935.

The boy was kept at rest until October 8 at which time physiotherapy was instituted in an attempt to improve motion in the knee joint. Walking and physiotherapy gave about 30 degrees motion and fair function in the left knee by November 30 when the patient was discharged. During the course of his active bleeding (September 5), the patient complained of abdominal pain beneath the right costal margin. This lasted for but 24 hours and there was no recurrence.

The studies done on the patient during his stay in the hospital included those above recorded and several other coagulation and bleeding times.

In all, there were 12 determinations of the coagulation time. These were as follows:

1935.	Time in minutes.
July 27	19
August 4	5
August 12	105+
August 25	90+
September 4	38
September 6	13
September 11	36
September 18	19
September 20	17
October 1	27
October 2	42
November 4	60+

On February 27, 1936, 5 months after the last bleeding episode had ceased, the coagulation time was 22 minutes. With the exception of the one in which the coagulation time was 5 minutes, the other 12 ranged between 13 minutes and 1 hour and 45 minutes. The bleeding time on all occasions was within the normal limits. The platelet count was normal. The clot retraction was normal on two occasions. On November 4, approximately 7 weeks after cessation of bleeding, the blood was observed not to clot for over 1½ hours, but the retraction was normal when the clot did form. The Wassermann and Kahn tests were negative on 3 occasions. On September 20, 1935, a Roentgen ray study of the left knee was reported as follows: "There is considerable swelling about the left knee joint and the suprapatellar bursa in particular. There is some destruction of the posterior articular surface of the patella with beginning squaring of the intercondylar space" (Figs. *A* and *B*). Dr. W. C. Hall, the roentgenologist, was of the opinion that while these findings are not absolutely typical of hemophilia they are undoubtedly due to this condition.[6,7] On October 9, there was somewhat more bone destruction about this joint, otherwise report was the same as previously noted. On November 6 this knee showed no bony ankylosis. On November 22, the wrists, shoulders, elbows, knees and ankles were examined and, with the exception of one small area on the right knee and the above named changes in the left knee, there was no evidence of bony change.

The boy has continued in good health since the cessation of the bleeding episode in September of 1935. There remains as evidence of his illness only deformity and restriction of motion in the left knee and a prolonged coagulation time.

Summary. A careful review of the literature has failed to reveal a single case of undoubted hemophilia in the negro. The case here reported, excepting for the family history, is typical of hemophilia. In spite of frequent nosebleed in 2 brothers and a maternal uncle and grandfather, the family history cannot be interpreted as the genealogy of a hemophilic. The patient was a very black negro without any ascertainable evidence of white ancestry who presented a history of immoderate hemorrhages from several sources since early childhood. He further showed rapid recovery following hemorrhage and had also the characteristic mischievous temperament which Bulloch and Fildes noted as being so constant that it might be regarded as almost a minor feature of the disease. He developed

A

B

FIGS. *A* and *B*.—Roentgen ray picture of the hemarthrotic left knee. *A*, Antero-posterior; *B*, lateral view.

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hemarthrosis of the left knee and joint changes typical of those found in hemophilics, though they are not pathognomonic. But 1 of the 13 coagulation time tests was within normal limits. This one was taken during a period of active hemorrhage. The coagulation time was still markedly prolonged 5 months after cessation of hemorrhage. The platelet count, the tourniquet test, the clot retraction, the Wassermann and Kahn tests were all negative.

It is generally recognized that a qualitative defect of the blood platelets interfering with proper coagulation of the blood exists in hemophilia. Studies are being made calculated to prove or to disprove the existence of such a defect in the platelets of this patient.

Conclusions. The case here cited is apparently the first instance of hemophilia in the full blooded negro to be recorded.

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PERNICIOUS ANEMIA IN THE NEGRO.

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Although anemia in the most bizarre forms develops in the negro, true pernicious anemia is considered to be quite rare, a fact borne out by the paucity of the literature on the subject and by the appearance of reports of small series of cases. Carr[1] reported 6 in 148 cases of pernicious anemia. Willson and Evans[2] found 8 mulattoes among 111 cases of pernicious anemia in the Johns Hopkins Hospital in 34,280 colored admissions. Eight cases were found by Traut[3] in a total of 256 cases of pernicious anemia at Cook County Hospital, where 33% of the admissions were colored. Matthews[4] encountered 2 instances among 4940 admissions to the

Veterans Bureau Hospital at Tuskegee, Alabama, in 5 years. From among 4503 negro admissions to the Peter Bent Brigham Hospital, Friedländer[5] reported 3 cases. Jamison[6] found the records of 12 cases in 121,000 colored admissions to Charity Hospital from 1920 to 1925.

Incidence. The decade 1926 to 1936 was selected because 1926 marks the inaugural of liver therapy in this hospital, the response to which affords an additional diagnostic proof. There were 247,239 colored admissions in this period, of which 43 cases were filed as pernicious anemia. We have rejected 25 of these because of insufficient data, and present below in tabular form 14 cases which we believe to be true pernicious anemia. A brief summary of 4 more presumptive cases, in which the data are too scanty to make them entirely acceptable, are added. The 14 cases represent an incidence of 1 case per 17,659 colored admissions.

In the same period, 277,324 whites were admitted. Of these, 187 cases are listed as pernicious anemia; 98 were taken to be true pernicious anemia and 89 were rejected by the same standards employed in selecting the colored cases. An incidence of 1 white case per 2829 white admissions is obtained, and 1 negro with pernicious anemia to 7 whites. The ratio of white to colored admissions in this period is 1.12 : 1.

The average age of the negro patients was 52 years, with extremes of 27 and 70 years. Nine of the patients were in the 5th or 6th decade.

Nine of the accepted patients were males, and 5, females. In the white group, the females predominated slightly.

Admissions into the hospital were slightly higher in the spring and summer months; this was also true of the white patients.

The duration of symptoms prior to admission averaged 9 months, with extremes of 2 months and 2 years.

Selection of Cases. All cases selected for this report showed achlorhydria. All had macrocytic hyperchromic anemia of marked degree which responded to liver therapy. They presented one or more of the symptoms of weakness, debility, numbness and paresthesias, breathlessness, palpitation, with or without edema, in the absence of cardiac failure, icterus, and cord changes.

Carcinoma of the stomach, pellagra, sprue, malaria, cirrhosis of the liver, hookworm and fish tapeworm infestation were apparently absent in the cases chosen. Cases having either a history of syphilis or a positive Wassermann were not believed to be acceptable because of the known mimicry of pernicious anemia by syphilis.

Clinical Data. The symptoms exhibited by the accepted cases, with the physical findings, are listed in Table 1.

In all 18 cases of accepted and probable pernicious anemia, the Wassermann test was negative. Further, the spinal fluid Wassermann and cell count were negative in 7; in the remaining cases it was not done.

TABLE 1.—SYMPTOMS AND SIGNS IN 14 CASES.

Symptoms.	No. cases.	Signs.	No. cases.
Weakness	14	Glossitis	9
Dyspnea	10	Icteric sclerae	8
Palpitation	9	Increased knee jerks	8
Paresthesias	9	Cardiac enlargement	5
Edema	8	Systolic murmur	5
Vertigo	7	Loss of vibratory sense	4
Diarrhea	6	Ataxia	3
Anorexia	5	Absent knee jerks	2
Abdominal distress	5	Babinski	2
Sore tongue	5		
Difficulty in walking	2		
Incontinence	2		
Precordial pain	2		

Achlorhydria was present in all cases, usually on more than one examination, and in 5 of the 18 cases, histamine was employed. In addition to the 8 cases showing clinical jaundice, of which 3 showed icterus indexes of 22, 40, and 50, respectively, there were 2 with an icterus index of 8.

For the sake of brevity, the characteristics of the erythrocytes on smear were omitted from the table of accepted cases, and reports of probable cases. All of the smears showed anisocytosis, poikilocytosis, and usually polychromatophilia, stippling and macrocytes. Some showed normoblasts and megaloblasts. Unfortunately, reticulocyte counts were not made frequently enough to make possible the presentation of a curve. However, after institution of liver therapy, for a varying number of days, in 8 of the 14 accepted cases, there were reticulocyte counts indicating bone marrow response. The maximum reticulocyte count available in the 8 cases were 4.5, 5, 6, 9, 9, 12, 17, and 29% respectively. Some of these obviously were not made at the time of the anticipated peak response.

The white counts in all cases but one, which was 6000, were below 4000, practically all of them being between 2000 and 3000. The neutrophil cells were usually from 30 to 40% of the total on admission, and with liver therapy increased to a normal percentage.

In Table 2 are presented data pertinent to the 14 accepted cases. Minimum and maximum erythrocyte counts, expressed in millions, and minimum and maximum hemoglobin values have been arranged for comparison. The total number of red counts done in these cases varied. In one, only 3 were done, in one 5, and 11 in a third. Of the remaining, two had 4 counts, two 6, two 8, two 9, and two 10 counts. Hemoglobin is recorded in grams per cent. In those instances where estimation was done by other than the Newcomer or Sahli method, the value was converted to grams on an arbitrary basis of 16 grams being 100%.

In addition to the 14 cases accepted as definite pernicious anemia, there were 4 in which the evidence available points to the probability of this disease, but in which the insufficient laboratory data do not justify an unqualified diagnosis. These cases are shown on page 755.

TABLE 2.—DATA IN 14 CASES OF PERNICIOUS ANEMIA IN NEGROES.

Case.	Sex.	Age.	R. B. C.		Hb. (gm.).		Color index.		Mean corpuscular volume.		Liver.				Year.
			Min.	Max.	Min.	Max.	Before therapy.	Peak response.	Before therapy.	Peak response.	Days before maximum response.	Oral, vials.	Parenteral, cc.	Transfusion, hospital day.	
1	F.	60	1 44	4 25	6 3	11 6	1 8	0 9	103 6	87 7	24	57	..	.....	1930
2	F.	67	0 41	1 5	3 2	6 4	2 5	1 3	.....	.....	26	79	..	2	1930
3	F.	27	0 44	2 9	2 4	6 4	1 7	0 7	.....	.....	42	152*	17	1	1930
4	F.	41	1 04	3 2	5 6	7 2	1 6	0 72	.....	.....	21	38	..	.....	1931
5	M.	43	1 97	3 8	6 4	..	1 1	..	100	100	18	56*	10	.....	1932
5a	..	..	2 38	4 25	11 2	12 8	1 5	0 9	.....	.....	37	..	29	.....	1935
6	M.	70	1 95	3 01	8 0	10 6	1 0	..	.....	.....	19	114	..	.....	1930
7	M.	73	1 5	3 07	4 0	9 5	1 3	0 9	.....	.....	51	85	..	9	1933
8†	M.	41	1 14	3 02	4 8	11 7	1 3	1 2	125	.....	28	..	53	.....	1933
8a	..	..	0 61	3 15	2 8	9 6	1 5	0 9	.....	.....	25	..	22	.....	1934
9	M.	43	1 46	3 43	5 6	12 0	1 2	1 0	.....	.....	36	..	43	.....	1935
10	M.	59	0 36	1 54	1 7	..	1 4	....	120	.....	16	..	31	.....	1935‡
11	M.	57	0 81	2 47	3 6	..	1 8	....	130	.....	16	..	27	1 and 2	1935
12	M.	56	0 62	3 60	5 3	..	2 6	....	.....	.....	51	84	..	7	1935
13	M.	51	1 99	4 2	6 4	11 0	1 0	0 79	130	89	30	90	..	.....	1929
14	F.	41	1 07	3 9	4 8	13 6	1 4	1 0	.....	.....	62	..	92	.....	1933
14a	..	..	2 86	4 0	8 0	..	1 8	....	.....	.....	59	110	31	.....	1935§

* Ventriculin.
† Followed weekly to July, 1936. 1 cc. intramuscularly weekly.
‡ Died of pneumonia.
§ Had taken 2 drams of liver extract daily. In 1934, red blood count was 4.10; hemoglobin 13.6.

Case Reports. Case 1.—I. H., male, aged 24, complained of abdominal pains, dyspnea, weakness, palpitation and diarrhea. Examination showed a glossitis, icteric scleræ, and absence of knee jerks. Red blood cells numbered 580,000, hemoglobin 2.2 gm., hematocrit 6.5%, mean corpuscular volume 112 cu. micra. The smear presented normoblasts, megaloblasts and 4.5 reticulocytes. Icterus index was 50. One transfusion was given. Patient developed pneumonia and died before further studies could be made.

Case 2.—T. G., male, aged 59, presented symptoms of sore tongue, vertigo, diarrhea, paresthesias, and inability to walk. On examination, there were glossitis, icterus, absence of vibratory sense, and spasticity of the lower extremities. Spinal fluid was negative. Red count was 1,790,000, hemoglobin 8.41 gm., color index 2.3, cell volume 108. Icterus index was 40. Clinical improvement took place in 17 days after one transfusion and 17 vials of liver extract. Red count increased to 2,630,000, with color index of 1.1 Necropsy showed enlarged, gray spleen and the liver contained some hemosiderin.

Case 3.—P. Y., male, aged 51, complained of inability to walk. Examination showed hypoactive reflexes. The red blood cells were 1,790,000, macrocytes were present on smear. After 210 vials of liver extract in 97 days, the red count mounted to 4,500,000.

Case 4.—O. H., female, aged 43, presented weakness, dyspnea, edema and difficulty in walking, with numbness of the feet. Examination showed hyperactive reflexes and positive Romberg. There were 670,000 red blood cells, with mean corpuscular volume of 112 cu. micra. After 5 days of liver, the reticulocytes were 13%. At the end of 3 weeks of liver therapy, the red count had risen to 1,780,000.

Discussion. An incidence of 1 colored to 7 white patients with pernicious anemia, on a basis of equally rigid selection, is not so great a difference between the two races as has been generally taught in the past. There may be two possible explanatory factors. It is conceded, by physicians who have had experience in both the Mid-west and the South, that pernicious anemia is less common here than in the former area. Second, due to the large percentage of negro admissions at Charity Hospital (45%), probably a larger number of this race is available for comparative study than in any other institution admitting both colored and white patients.

It is felt that a selection on the basis outlined above is sufficiently rigid to warrant acceptance of these cases as true Addisonian anemia. In the 14, there occurred a macrocytic anemia with high color index and achlorhydria, and response to liver extract, in the absence of other conditions simulating the picture of pernicious anemia. It is admitted that the blood picture in each case should have been followed to normal levels, and also that in some, the liver therapy was inadequate. However, this could not be avoided because deplorable overcrowding makes prolonged hospitalization impossible. Too, the negro is very prone to desert when he feels subjectively improved.

Four of the 14 cases chosen have been studied personally by us, and we have followed one through a relapse while he was unable, for financial reasons, to procure liver. On the initial admission his extreme ataxia compelled him to be carried to the hospital. He now walks unaided to the hospital each week to receive an injection of liver extract.

Striking is the frequency of cord changes as manifested by subjective complaints of numbness, ataxia, walking difficulties, and the finding of abnormal reflexes, and loss of vibratory sense. These occurred in a higher percentage of cases in this series than would be seen in white patients. This is readily explained by the fact that, generally speaking, the pathology of disease is more advanced in the negro, on admission, than in the white.

It is universally accepted that pernicious anemia, rarely, if ever, occurs in the full-blooded negro. This is probably true. Of our series, we know definitely that the 4 we observed were of mixed white and negro blood, and it is quite possible that the rest were also.

Summary. 1. Fourteen acceptable and 4 presumptive cases of pernicious anemia have been found in almost a quarter million negro admissions to Charity Hospital.

2. The low incidence of pernicious anemia in the white admissions to this hospital gives a ratio of 1 colored to 7 white patients with this disease.

3. The symptoms of the negro are almost the same as of the white patients, differing only in degree, due to the notorious self-neglect of the former race.

4. Pernicious anemia probably does not occur in the pure blooded negro, though in only 4 of our cases has a mixed ancestry been established.

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ADDISON'S DISEASE IN THE NEGRO.

Report of Seven Cases.

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Over 300 cases of Addison's disease are reported annually in the registration area of the United States.[1] It is generally accepted that the disease is prone to occur more frequently in members of the

laboring class. At necropsy, tuberculosis has been the etiologic factor in the great majority of cases.[2] Considering the relatively high incidence of tuberculosis among Negroes, and the heavy manual labor by which many of them earn their livelihood, it is surprising that only 7 cases[3] of this syndrome in the colored race appear to have been reported. A casual inquiry at a few neighboring hospitals has brought to light 6 previously unreported cases which we are privileged to add to the 1 recently observed at the University Hospital. This would seem to indicate that this clinical picture is more frequent among Negroes than is generally appreciated.

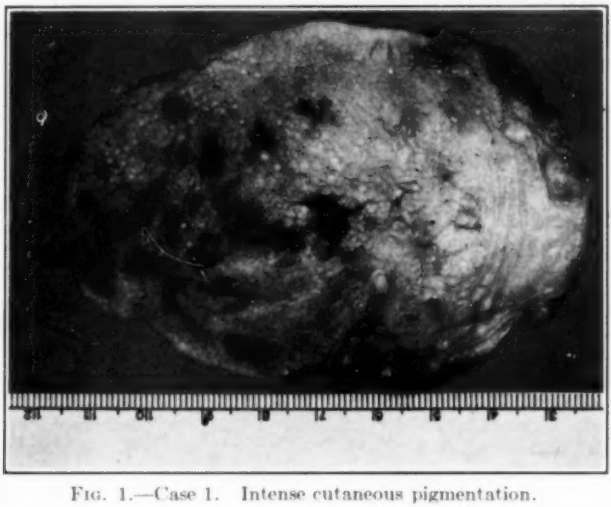

FIG. 1.—Case 1. Intense cutaneous pigmentation.

Case Abstracts. CASE 1.—(University Hosp. No. 35-21267). A 60-year-old ebon Negress was admitted to the service of Dr. Alfred Stengel in an extremely weakened condition, the increasing pigmentation of the skin having been noted for 7 months. Her husband insisted that she had previously been a "high-yellow" Negress. For 2 months she had frequently vomited, lost 23% of her body weight, and become increasingly fatigued, necessitating bed confinement at home under her physician's care 3 weeks before hospitalization.

Upon admission, physical examination revealed an extremely weak, intensely pigmented, elderly Negress, temperature 98.2°, pulse 84, respiration 34, several pigmented nævi of the face, general loss of muscle tone, diffuse faint striæ of the skin, patchy buccal and lingual pigmentation, hypotension (65/45), and fine moist râles at the apex of the left lung. Urinalysis, blood count, Wassermann test, urea nitrogen and sugar determinations were not abnormal. The blood sodium (130.7 m.eq./L.) and chloride (89.4 m.eq./L) were diminished. No acid fast bacilli were found in a single sputum examination. A tentative diagnosis of Addison's disease with active pulmonary tuberculosis was made, and large doses of potent adrenal cortex extract and sodium chloride were administered. The patient gradually lapsed into coma, with steadily falling blood pressure and terminal hyperpyrexia (106°), death supervening 41 hours after admission to the ward.

AUTOPSY: the adrenals were replaced by fibrocaseous tuberculous masses, accompanied by mesenteric tuberculous lymphadenitis and bilateral apical fibrous tuberculosis. An atrophic thymus persisted. The previously mentioned pigmentation of the skin and mucosal surfaces was also faintly visible in the urinary bladder.

FIG. 2.—Case 1. The tongue, showing patchy pigmentation.

CASE 2.—(Presbyterian Hosp., New York). A 54-year-old Negress was admitted complaining of weakness, loss of weight, and increasing skin pigmentation for 4 months. At postmortem examination bilateral adrenal tuberculosis, obsolete pulmonary tuberculosis, and miliary tuberculosis were demonstrated.

CASE 3.—(Presbyterian Hosp., New York). A 33-year-old Negro returned to the hospital 3 years after removal of a tuberculous kidney, having noticed skin pigmentation for 1 year. Three weeks before admission he ceased work because of rapidly developing weakness, anorexia and vomiting. At autopsy there were found obsolete pulmonary tuberculosis, bilateral adrenal tuberculosis, tuberculous pneumonia and peritonitis.

CASE 4.—(Presbyterian Hosp., New York). A 39-year-old Negro came to the hospital stating that he had "grown three shades darker in the past year," and had become quite weak during the previous 6 weeks. Tuberculosis was clinically evident in the left kidney, the seminal vesicles and the right epididymus. Developing severe adrenal insufficiency, the patient was successfully treated with sodium chloride and discharged. Seven months later he died suddenly, presumably due to hypoglycemia which he had exhibited previously, but an autopsy was not performed.

CASE 5.—(Bryn Mawr Hosp., No. 019754). A 65-year-old Negro was admitted to the service of Dr. J. L. Spangler with active pulmonary and epididymal tuberculosis, first recognized 3 months previously. The chief complaint was the nightly occurrence of brief clonic spasms of the leg muscles, with general soreness and weakness necessitating confinement in bed for a fortnight. Increasing pigmentation of the skin for several months was affirmed by the patient's pastor. Asthenia, emaciation and hypotension (85/58) were the paramount physical findings, while during the 3 weeks before death there appeared anorexia, vomiting, hiccoughs, incoherence and hypomania. At autopsy the adrenals were found to be entirely destroyed by caseous tuberculosis, with less extensive lesions of the lungs and genital tract.

CASE 6.—(Philadelphia General Hosp., Autopsy No. 21967). A 26-year-old Negress was admitted to the service of Dr. H. D. Jump in hypoglycemic coma, with history of general malaise, weakness, loss of weight and skin pigmentation for 1 year. Glucose therapy failed to alleviate the semistuporous state of the patient, and she died 6 days later. Fibrocaseous tuberculosis of both adrenals was found at autopsy.

CASE 7.—(Philadelphia General Hosp., Autopsy No. 29416). A 21-year-old Negro, with old Pott's thoracic deformity and history of previous hypoglycemic coma, was admitted to the service of Dr. W. E. Robertson with severe abdominal pain and vomiting, the second exacerbation of these symptoms. He presented hypotension (80/40), pigmentation of the mouth and hands, and slightly subnormal blood chloride level. He died 3 days later of acute adrenal insufficiency. At autopsy no pulmonary tuberculosis could be demonstrated, but the vertebrae and both adrenals were extensively involved.

Discussion. The comparison of the 14 reported cases of Addison's disease in the Negro present many interesting conclusions. Eight of the patients were males, 6 were females, and with one possible exception (Case 4), all died with signs of adrenal insufficiency. Their ages ranged from 21 to 65 years, the average being 44 years at death. Increasing skin pigmentation in 12 of the 14 cases had been recognized by the patients or their friends for several months before hospitalization. Anorexia, vomiting, loss of weight and increasing weakness were prominent features of almost every history. Hypotension was pronounced in each case where blood pressure readings are given. The maximum duration of life after recognition of the disease was 7 months, while 6 of the victims succumbed within 8 days after hospitalization. Tuberculosis was the etiologic agent in each of the 11 cases which came to autopsy, 1 case (that of King and Mulholland) also showing a congenital absence of one adrenal.

Summary. 1. Seven cases of Addison's disease among Negroes are presented, bringing the total number in the literature to 14.

2. The occurrence of this syndrome in the Negro would seem to be much more frequent than the recorded cases would indicate.

3. The diagnoses as a rule were made in the late or terminal stages, but otherwise the symptomatology differed in no way from that usually seen in white patients with this syndrome.

4. Tuberculosis was the etiologic agent in each of the 11 cases which came to autopsy.

We wish to express our appreciation for the privilege of presenting these additional cases to Dr. Robert Loeb (Cases 2, 3 and 4), to Dr. John L. Spangler (Case 5), and to Drs. Jump, Robertson and Welty (Cases 6 and 7). The last 2 cases are presented in more detail from the standpoint of hypoglycemia by Dr. John Welty in the following article.

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HYPOGLYCEMIA IN ADDISON'S DISEASE.

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The occurrence of hypoglycemia in affections of the adrenal glands has been noted both clinically and experimentally by many observers; current textbooks, however, fail to mention it. Bierry and Malloizel,[1] in 1908, noted reduction of blood sugar values in dogs following adrenalectomy; Borges[2] confirmed this observation 2 years later and in addition reported 3 cases of Addison's disease, all of which presented low blood sugar levels. Janney and Isaacson,[3] in 1918, stated that hypoglycemia frequently resulted from hypoendocrine function, showing experimentally that it developed regularly after thyroidectomy and calling attention to its frequent occurrence in destructive lesions of the adrenal glands. In an extensive review of Addison's disease in 1925, Rowntree[4] noted the very frequent finding of a fasting blood sugar below the normal level and stated that in 2 of his cases it had reached the low figure of 45 mg. %. Chapman[5] reported a case in 1926 which presented a flat glucose tolerance curve and Wadi[6] later called attention to the similarity of symptoms in Addison's disease and hypoglycemia, describing at that time a case of the former with convulsions relieved by dextrose administration; diagnosis in this case was proved by necropsy. Turner[7] and Porges and Adlersberg[8] also reported cases showing marked increase in the carbohydrate tolerance. Wauchope's[9] recent review of hypoglycemia summarizes the knowledge to date upon this subject.

A few observers have disagreed with these findings. Sakaguchi[10] noted no definite hypoglycemia in 5 cases of Addison's disease and later was unable to produce this phenomenon by removal of the adrenal glands in rabbits. He concluded that adrenalectomy has no great influence upon the sugar assimilating power of the organ-

ism. Rosenow and Jaguttis[11] believed, after study of a patient and a critical survey of previously reported cases, that hypoglycemia was not a constant symptom of Addison's disease; these workers, however, noted the paradoxical hyperglycemia following adrenalin administration which was later observed by Turner.[7]

The following proven cases of Addison's disease are reported because they showed evidence of marked hypoglycemia with coma relieved by dextrose administration, and because in one case symptoms of the increased sugar tolerance overshadowed those of the destructive adrenal lesion and made the differential diagnosis very difficult.

Case Reports.—Case 1. J. A., a 21-year-old, American born Negro, was admitted to this hospital (service of Dr. W. E. Robertson), on February 18, 1935, complaining of abdominal pain and vomiting for 3 days. The history of his present illness dated back to early December, 1934; following a "cold" of 2 days' duration manifested by cough, headache, and vomiting, the patient rather suddenly went into deep coma. A hospital examination of the blood revealed the glucose level to be 40 mg. % with a carbon dioxide combining power of 30. He was given 100 cc. of 50% glucose in normal saline solution by intravenous injection at once; during this procedure the patient regained consciousness rather dramatically and talked rationally. He remained in the hospital 14 days, during the first 2 of which a mild fever and cough were present. He was discharged in apparently good condition with the final diagnosis of hypoglycemia and acute bronchitis. It was believed that the former was incidental and precipitated by starvation during the upper respiratory infection. No additional studies were done. Following discharge he remained well until 11 days before admission at which time he vomited without apparent reason after a breakfast of hominy grits. Following this there were no symptoms until 3 days before admission when, in the midst of a breakfast of oatmeal, he suddenly and without warning vomited. While vomiting he felt sharp pain in the midepigastrium which did not radiate and which disappeared within a few minutes. The same course of events occurred several times during the next few days. Dull, frontal headache accompanied the gastro-intestinal upset.

The family history was negative. Review of the past history revealed that he had been "hunchbacked" since the age of 4. He did not believe that there had been any change in the color of his skin which he stated had always been very black. He had had rare heterosexual experiences. Abdominal upsets with vomiting had been noted frequently for several years.

Physical examination revealed a small, kyphotic Negro with a peculiar "mouthy" speech, lying in bed in no apparent pain or distress. Mentally he was clear, alert and coöperative but of low intelligence, answering question in monosyllables. The skull was small, long and symmetrical, the jaw markedly prognathous. Prominent lips protruded beyond the very flat nose. The skin was extremely black. Examination of the eyes revealed nothing externally but the fundi presented bilateral temporal pallor. The teeth were dirty, poorly developed and thin with very pointed canines. The tongue was pale pink with irregular patches of black pigmentation; similar areas were present on the buccal mucosa and palate. Examination of the back showed an extreme dorsal kyphosis and lumbar lordosis, the spine being practically doubled upon itself. The chest was deep and deformed and the lower ribs rested on the pelvic brim. The heart and lungs seemed normal. The blood pressure was 95 systolic and 75 diastolic bilaterally. Slight midabdominal tenderness was noted. The external genitals

were normal. The narrow, short hands were in marked contrast to the long tapering fingers. Palms, soles and nail beds were extremely black.

Urinalyses, urea clearance tests and phenosulphonphthalein tests were negative as was the blood Kahn reaction. Erythrocytes varied from 3.8 to 4.1 million. The leukocyte count averaged 15,000 (lymphocytes 60% or more). Blood plasma chlorides fluctuated between 550 and 580 mg. % (as sodium chloride). Blood calcium and phosphorous levels were normal. Blood urea nitrogen varied from 25 to 35 mg. %.

Blood sugar examination on admission showed a fasting level of 68 mg. % (reducing power of tungstic acid filtrate determined by the Folin-Wu method). A number of glucose-tolerance tests were done, all of which showed a practically flat curve. A representative 3-hour curve after $1\frac{1}{2}$ gm. of glucose per kg. administered to the fasting patient by mouth was:

Fasting	75 mg.%	2 hours	75 mg.%
30 minutes	72 mg.%	3 hours	72 mg.%
1 hour	72 mg.%		

A typical 6-hour curve under the same conditions was:

Fasting	72 mg.%	3 hours	70 mg.%
30 minutes	77 mg.%	4 hours	63 mg.%
1 hour	80 mg.%	5 hours	59 mg.%
2 hours	80 mg.%	6 hours	58 mg.%

Roentgen-ray examination of the skull was negative. There was no Roentgen evidence of adrenal calcification. Chest films showed nothing suggestive of pulmonary tuberculosis. The basal metabolic rate, carefully corrected for the patient's deformity, was −19. Other laboratory studies were essentially negative.

Following the first few days on the ward the patient was in good condition, ambulatory, and was kept in the hospital solely for the purpose of further studies. The systolic blood pressure varied from 80 to 90 and the diastolic from 50 to 60. A tentative but questioned diagnosis of Addison's disease was made. A salt-free diet for the purpose of proving this was considered but not instituted because cortical extract could not be obtained for use in a possible crisis. The patient was discharged April 10, 1935.

He continued to feel well until May 5, 1935, when there was recurrence of the vomiting and transient abdominal pain. Three days later he returned to the hospital where examination was as before. Admission blood sugar was 77 mg. %. Blood pressure was 90/60. On May 10, the patient rather suddenly went into profound shock with a cold clammy skin, subnormal temperature and a cardiac rate at the apex of 30 beats per minute. Soon he was in deep coma and the corneal reflex was unobtainable. Intravenous administration of 1000 cc. of 10% glucose in normal saline was begun; he reacted almost at once and within 30 minutes was fully conscious. Eighteen hours later, during which time cortical hormone had been obtained and administered together with glucose and saline, shock was again prominent. The patient failed to respond and died within the hour.

Necropsy (Dr. R. P. Custer) revealed bilateral fibrocaseous tuberculosis of the adrenal glands. Histologically, there were a few very small islands of cortical and medullary tissue remaining. So-called "status thymico-lymphaticus" was also noted with marked hypoplasia of the heart, aorta, and peripheral arteries. There was a healed primary tuberculous pulmonary complex. The right renal lymph nodes presented active fibrocaseous tuberculous lymphadenitis. A healed Pott's disease was present involving the upper thoracic region.

CASE 2.—V. M., a 26-year-old, American born Negress, was admitted to this hospital (service of Dr. H. D. Jump), on June 16, 1930, in a state of semicoma. According to the history obtained from relatives she had been

complaining of weakness, weight loss and malaise during the preceding year. A perverted appetite for sweets had been prominent and shortly before admission she had consulted a physician. He had told her that the diet contained too much carbohydrate food and advised one consisting chiefly of vegetables which the patient followed rather faithfully. It had also been noted that the color of the skin had been getting darker for the past year, it now being dark shiny black whereas it had originally been light brown. Aside from these symptoms the patient had been well until the day of admission when she was found by a member of her family in an unconscious state.

Examination revealed a confused, negativistic, semicomatose colored female. The skin was ebony black and glistening with the nail beds deeply pigmented. The mouth was badly infected but no pigment deposits were seen. There were palpable cervical lymph nodes. The pupils were dilated but reacted promptly to light. Examination of the lungs and heart presented nothing unusual. Blood pressure was 90/60. The admission blood sugar was 50 mg. % with a carbon dioxide combining power of 43. Other laboratory studies were essentially negative. Following intravenous glucose the patient responded and improved temporarily. However, she later became apprehensive and semistuporous; death occurred 6 days after admission.

Necropsy (Dr. J. O. Collins) revealed bilateral fibrocaseous tuberculosis of the adrenal glands and findings suggestive of "status thymico-lymphaticus." The pathologist stated that practically all the adrenal cortex, bilaterally, was destroyed but did not comment upon the amount of adrenal medullary tissue present.

Discussion. In these 2 cases of Addison's disease hypoglycemia was the outstanding manifestation causing coma subsequently relieved by dextrose administration. Case 1 was a particularly difficult diagnostic problem; it was seen by a number of competent endocrinologists none of whom could definitely decide whether the pathologic lesion was in the adrenal gland, the pituitary gland or the pancreas. The relatively normal serum chloride in Case 1 deserves comment. It is well known that patients with destructive adrenal lesion and adrenalectomized animals respond dramatically to sodium chloride. However, such individuals show low blood chlorides. In this case the normal serum chloride level strengthens the belief that the glucose was specific.

Turner[7] attributes hypoglycemia in Addison's disease to destruction of the adrenal medulla; the fact that adrenalin administration with glucose causes hyperglycemia lasting several hours favors this theory. In normal individuals there is a delicate balance between insulin secretion which lowers blood sugar and adrenalin secretion which raises blood sugar. This balance is destroyed in lesions of the adrenal medulla, resulting in hypoglycemia. Whether or not this occurs in Addison's disease probably depends primarily on the amount of functioning adrenal medulla present. Such a view explains why all cases do not present this finding.

We believe that with the symptom of hypoglycemia present Addison's disease should always be considered in the differential diagnosis. Hyperinsulinism and Simmonds' disease are perhaps the two affections most difficult to rule out. The former can frequently be differentiated by the absence of the typical symptoms

of pigmentation and hypotension. In addition, the glucose tolerance curve of the two diseases differ rather characteristically. The 6-hour curve of typical hyperinsulinism tends to become progressively lower and shock is usually observed before completion of the test; the curve of Addison's disease is relatively flat, does not decrease sharply and shock is rare unless there are complicating factors such as intercurrent infection or starvation which may deplete the body glucose supply. The glucose tolerance curve of Simmonds' disease resembles somewhat that of Addison's disease. However, extreme cachexia, loss of sexual function, marked depression of the basal metabolic rate (with hypothermia and hypotension), together with loss of teeth and hair (axillary and public) are usually present, thus aiding in differentiation.

Summary. 1. Two cases of Addison's disease with hypoglycemic coma as a prominent manifestation are reported.

2. Hypoglycemia in Addison's disease strongly suggests involvement of the adrenal medulla.

3. The characteristic difference in the glucose tolerance curves of hyperinsulinism and Addison's disease is shown.

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OBSERVATIONS ON THE EFFECTIVENESS OF PROTAMINE INSULIN.

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During recent months several papers on the use of protamine insulin have appeared in addition to Krarup's monograph from the

Steno Memorial Hospital.[1–7] Up to this time the following observations have been made about protamine insulin: (1) It acts more slowly than regular insulin, so that if given shortly before a meal the blood sugar will be found to rise considerably after the meal prior to the insulin becoming effective. (2) It acts for a much longer time, so that as long as 24 hours after the injection of this insulin the blood sugar may be normal or even below normal, thus preventing any early morning rise of the blood sugar so often necessitating a midnight dose of the regular insulin. (3) Possibly on account of its slow action, it is accompanied by fewer hypoglycemic reactions, and in most cases it affords a longer period of warning before the more severe symptoms become evident. (4) It steadies the blood sugar level, so that there is less variation from hour to hour than with the regular insulin. (5) It shows its full effect only after from 3 to 5 days from the time of the first injection, so that when protamine insulin is first used, hyperglycemia and glycosuria may ensue for several days. From the last observation it is clear that increases in dosage should be made at well-spaced intervals.

Up to the present, protamine insulin has been given in four ways: (1) To those patients requiring not over 40 units daily, one dose before breakfast has usually been sufficient for the entire 24 hours. (2) In those patients requiring a larger amount, protamine insulin has been given twice daily. (3) In the evening only with regular insulin before breakfast. (4) In the morning before breakfast with a dose of regular insulin administered at the same time. The exact times at which these injections have been given have varied depending upon the distribution of food and exercise during the day. The protamine insulin, whether given in the morning or in the evening, has prevented the early morning rise in blood sugar even in those patients requiring the largest amount of insulin.

Present Study. Our experience with protamine insulin extends over a period of 8 months, with a total of 45 patients studied. Our results have, in general, been similar to those already reported.

Patients on Large Doses of Insulin. The earliest patients in whom we used protamine insulin were those who required from 60 to 90 units of insulin daily, and who were so unstable that it was quite impossible to maintain them on the old insulin without frequent hyperglycemia or hypoglycemia. These patients had been taking insulin before breakfast, before supper and at midnight. The protamine insulin was first given 2 hours before breakfast and 2 hours before supper. In no case were the amounts of protein, fat or carbohydrate in the diets altered during the period of standardization with protamine insulin.

In Fig. 1 is shown the effect on blood sugar of protamine insulin as compared with that of regular insulin in a patient in this group. It is evident that there is much less variation in the blood sugar level throughout the 24 hours and that the early morning hyper-

glycemia is entirely prevented. All the patients reported a definite subjective improvement. This consisted in an increase in strength and alertness, with a desire for increased activity.

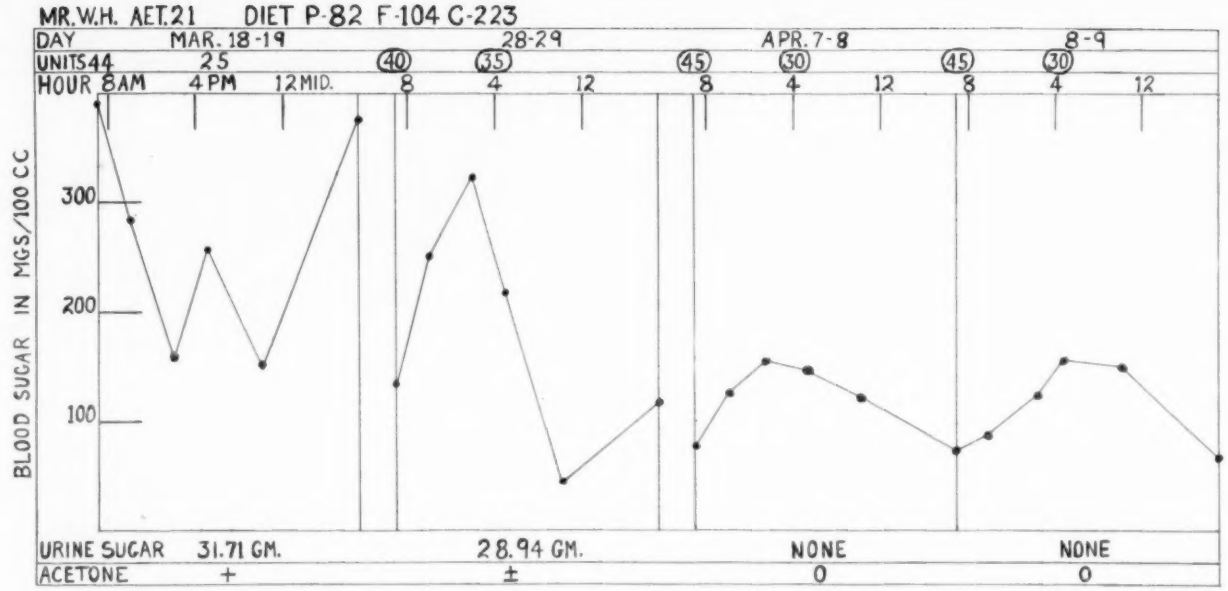
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FIG. 1.—The 24-hour blood glucose curves in a severe diabetic on regular and protamine insulin. In the left-hand curve note the heavy glycosuria and wide fluctuations of blood glucose in contrast to the absence of hyperglycemia and glycosuria with protamine insulin. This patient has purposely been kept on a high carbohydrate diet because of previous malnutrition and a marked lipemia. Numerals within circles indicate protamine insulin. Acetone is recorded qualitatively in the 24-hour specimen. Venous blood for sugar determinations was taken at 7 and 10 A.M. and 2, 5 and 10 P.M. *P, F, C* indicate the daily allowance in grams of protein, fat and carbohydrate, respectively.

The hyperglycemia and glycosuria which have been reported as following the first use of protamine insulin have been present in several of our patients, but was marked in only one. This patient was a young woman of 22, slightly overweight, with diabetes of 15 years' duration, taking from 80 to 90 units of insulin per day. There was an increase in her blood sugar to 480 mg. per 100 cc. of blood and an excretion of 155 gm. of glucose on the fourth day of protamine insulin, on a diet of 167 gm. of available glucose. The urine also contained a considerable amount of acetone and aceto-acetic acid. It seemed necessary to give her regular insulin in the morning and protamine insulin in the evening, and on this combination she was maintained satisfactorily.

Without exception the early morning blood sugar rise, even in those patients requiring large amounts of insulin, has been prevented. In only 3 of our patients have we felt that it was more satisfactory to give regular insulin in the morning and protamine insulin in the evening. In 3 patients protamine insulin was discontinued altogether, in 1 because of a severe reaction which accompanied overexertion and overindulgence in alcohol, and in 2 because of lack of coöperation.

During the period of regulation on protamine insulin, when there was hyperglycemia and glycosuria a moderate amount of acetone was present in the urine. However, after adjustment, we have found acetone only occasionally, as in the case of patients on regular insulin.

Aspects of Replacement. The amount of protamine insulin necessary to replace regular insulin has been found by us to vary considerably. Patients who required over 50 units of regular insulin daily have required practically an equal amount of protamine insulin to replace it. On the other hand, patients taking from 15 to 50 units daily have required definitely less of the protamine insulin. The average daily amount of regular insulin taken by all the patients studied was 37 units, while the average amount of protamine insulin necessary to replace this was 30 units. The average number of injections daily was reduced from 2.3 to 1.4.

In patients using 2 doses of protamine insulin various attempts have been made to distribute it throughout the 24 hours, so that there would be the least possible interference with their daily lives. While the régime was not satisfactory in all cases, in some we found that if five-sixths of the daily amount of protamine insulin were given 1 hour before breakfast and one-sixth at 7.30 P.M., a satisfactory balance was obtained. The morning dose was available for the lunch and supper, while the evening dose maintained the patient during the night and through breakfast. This obviated the necessity of arising 2 hours before breakfast and of taking a dose of insulin in the middle of the afternoon.

Transfer to Protamine Insulin Without Hospitalization. Our experience with the hospitalized patients was such that we felt that those in the out-patient clinic already adjusted on 2 doses of regular insulin daily could be transferred successfully to 1 dose of protamine insulin without the necessity of entering the ward. We have made this change in over 30 patients. It was possible to do this by giving an amount of protamine insulin 1 hour before breakfast equal to the morning dose of regular insulin, at the same time omitting the evening dose. After several days some of the patients have required an increase in this dose, though in none of the group

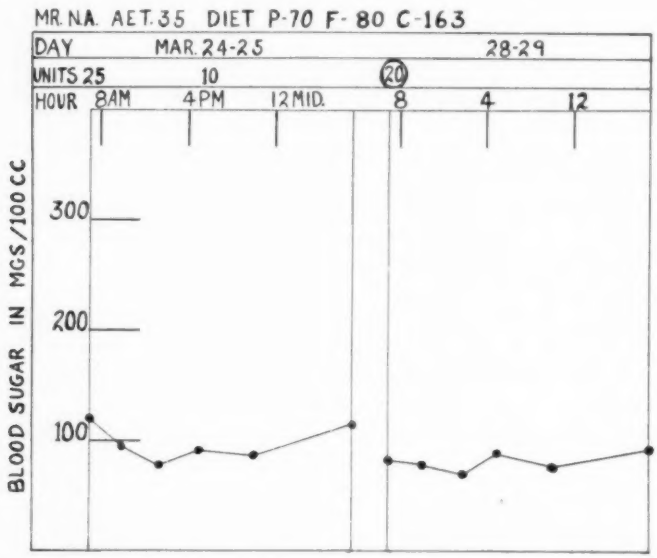

FIG. 2.—The effectiveness of one dose of protamine insulin in a moderately severe diabetic, previously controlled with 2 doses of regular insulin. Note the decrease in units required. Venous blood for sugar determinations was taken at 7 and 10 A.M., and 2, 5 and 10 P.M. *P, F, C* indicate the daily allowance in grams of protein, fat and carbohydrate, respectively.

has it been necessary to give an amount of protamine insulin equal to the total of the 2 doses of regular insulin formerly given. On account of the slow action of protamine insulin we have found that if 20% of the total daily carbohydrate is given at breakfast and 40% at each of the other meals, a better balance can often be maintained. Small supplementary feedings during the morning, afternoon and evening are sometimes an aid in affecting this.

Only occasional slight hypoglycemic reactions, and no other untoward incidents of any sort have occurred in this group of patients. Furthermore, every patient in this group has felt better on the protamine insulin. We have not yet given protamine

insulin without hospitalization to patients taking over 40 units of regular insulin daily.

In Fig. 2 are shown the blood sugar determinations before and after a change from 2 doses of regular insulin to 1 dose of protamine insulin daily.

It is possible with care to adjust on protamine insulin patients in the clinic who have not had previous experience in controlling their diabetes. When such patients cannot be hospitalized they can be given a larger dose of protamine insulin than of old insulin without fear of reaction. Our experience with this type of case has been limited, but satisfactory.

Hypoglycemic Reactions. Hypoglycemic reactions have been reduced both in number and in severity. They have occurred mostly in patients taking large doses. On all occasions except one, they have reacted promptly to sugar in the form of glucose or orange juice. A man, aged 29, taking 85 units of protamine insulin daily, had a severe reaction in the early morning following an evening of dancing and of somewhat excessive use of alcohol. This reaction will be reported in detail at a later time. On the day before his severe reaction he had stated in clinic that he had never felt so well during the 12 years of his diabetes, nor had he had so few reactions as in the previous weeks while using protamine insulin. Attention may be called to the fact that he had been very unstable on regular insulin.

As has been noted by others, we have found that hypoglycemic reactions following protamine insulin may occur at any time up to 24 hours after the latest preceding dose. They are sometimes only temporarily relieved by sugar, recurring in 1 to 2 hours and requiring further sugar for their control.

Comparison of Effect of Regular Insulin and Protamine Insulin on Blood Sugar. To determine the interval of time between the injection of protamine insulin and its first effect on the blood sugar as compared with the regular insulin, 12 patients were studied. These patients having had no food or insulin since the preceding day were given regular insulin and protamine insulin on succeeding days. Seven blood sugar determinations by Benedict's method were done at 15-minute intervals on arterial blood from finger prick. The insulin was given immediately after the first specimen of blood had been taken, so that 1 determination was done before and 6 after the insulin was administered. Equal doses of regular insulin and protamine insulin were given to each patient. These approximated the regular morning dose of insulin and varied from 10 to 40 units. On 1 patient the examinations were repeated with 10 units on each of the first 2, and 30 units on each of the second 2 examinations, so that in all there were 26 tests on the 12 patients.

The results of these examinations were studied in order to determine (1) the duration of time between the insulin injection and the

beginning of the consequent fall in the blood sugar, and (2) the amount of the fall in blood sugar which occurred in the 90 minutes during which blood sugar determinations were done. In Table 1

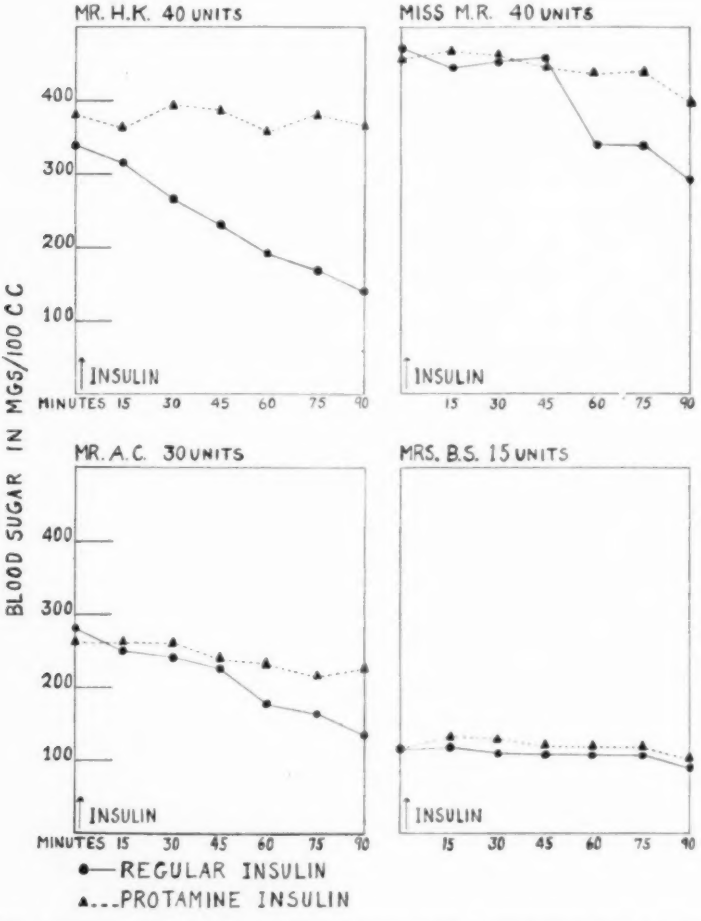

FIG. 3.—Comparison of the rapidity of action after subcutaneous administration of regular insulin and protamine insulin on successive days. The same dosage was used with both, and the amount coincides with the dose of regular insulin previously used before breakfast. Arrows indicate the injection of insulin after the fasting level had been obtained. Note the sharp drop after regular insulin in Mr. H. K., and the delay of 45 minutes in Miss M. R. In both instances no appreciable effect from protamine insulin was evident until 90 minutes had elapsed. The failure of Mrs. B. S. to respond is probably a reflection of the normal fasting level.

is shown the elapsed time between the injection of insulin and the first definite fall in blood sugar.

It is quite evident that the regular insulin acts more rapidly.

In 7 examinations with regular insulin the first definite decrease in blood sugar occurred at the end of 15 minutes after the insulin was injected, while following protamine insulin, only 2 showed any effect in 15 minutes and 10 showed the first effect in from 30 to 60 minutes. In Fig. 3 are shown the blood sugar curves on regular insulin and on protamine insulin in 4 patients who received from 15 to 40 units. One patient did not react until 90 minutes after receiving protamine insulin. The patient on whom the test was repeated with larger doses of insulin showed the first effect with 10 units of regular insulin in 30 minutes and with 10 units of protamine insulin in 60 minutes. When the test was repeated with 30 units the effect was evident in 15 and 45 minutes respectively. In only 1 patient did the protamine insulin react more rapidly than the regular insulin. It is evident, therefore, that while protamine insulin is slower acting than the regular insulin, there is much variation in the time at which each shows a definite effect on the blood sugar.

The average total decrease in blood sugar during the 90-minute period following the injection of regular insulin was 99 mg. per 100 cc., or 36% of the original fasting blood sugar. After protamine insulin the average fall in blood sugar was 28 mg. per 100 cc., or 12%. It would appear that, in accord with clinical observations, the action of the protamine insulin is definitely postponed as compared with regular insulin.

The more recent preparations with calcium and zinc appear to be more effective than the original protamine insulin. However, further experience will be necessary before their superiority can be expressed statistically.

Summary. From our experience it appears that protamine insulin presents a very definite improvement over regular insulin in the treatment of diabetic patients on a balanced diet. It is possible to reduce both the number of units and the number of injections daily and at the same time to maintain the blood sugar at a more constant level. The feeling of general improvement reported by the patient is gratifying.

Patients who have been controlled with less than 40 units of regular insulin may be satisfactorily transferred to protamine insulin without hospitalization. In this group, rearrangement of the carbohydrate distribution offers definite advantages. Thus, one-fifth of the day's allowance at breakfast and two-fifths at noon and night shifts the metabolic burden so as to coincide with the delayed action of protamine.

In the group of patients on 2 doses of protamine daily, five-sixths of the day's dosage was administered in the morning and one-sixth at night, spacing the doses 12 hours apart.

The influence of protamine insulin on blood sugar is definitely delayed as compared with that of regular insulin.

TABLE 1.—THE EFFECT ON BLOOD SUGAR OF PROTAMINE INSULIN COMPARED WITH THAT OF REGULAR INSULIN.

Number of minutes after insulin injection at which blood sugar decrease was first noted	15	30	45	60	75	90
Number of examinations with regular insulin	7	3	1	2	0	0
Number of examinations with protamine insulin	2	3	4	3	0	1

The incidence of significant decreases in blood sugar at intervals after administration of regular insulin and protamine insulin is shown. Percentage of fall from the fasting value was much greater after the former.

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NUCLEAR SIZES IN GROWTH DISTURBANCES.

WITH SPECIAL REFERENCE TO THE TUMOR CELL NUCLEUS.

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THE sizes of the cells of a given tissue do not vary irregularly, but they depend largely, as has been shown conclusively, upon the laws of growth (Jacobj, 1935). If a cell divides by *mitosis*, there arise two daughter cells, each of which is of the original size of the mother cell. If the daughter cells divide again, there arise four granddaughter cells, each of which is of the original size of the daughter cells. The total volumes of the three generations are therefore in the proportion of 1:2:4 (Fig. 1, I). If a cell grows by *amitosis*, *i. e.*, by nuclear division without cytoplasmic division, the same proportion results. Also in this case there arise daughter cells of double and granddaughter cells of fourfold the size of the mother cells (Fig. 1, II). The same is true also in so-called "*inner division*" (Heidenhain), *i. e.*, in simple enlargement of a cell without nuclear or cytoplasmic division. Also in this event we observe the proportion of 1:2:4 (Fig. 1, III). As all genuine growth is due to mitosis,

amitosis or "inner division," a given tissue only contains cells whose volumes are within a *geometrical line*. Heidenhain (1923), who was the first to derive this law, therefore called it the *law of growth in constant proportions*.

The reason that this law had not been discovered before is undoubtedly due to the fact that only mean figures had been considered. Only when Jacobj (1925) introduced the variation statistical method into cellulometry could this law be verified. Since the findings of Jacobj have been corroborated in many tissues of animals and plants (Clara, 1928–1933; Voss, 1928; G. Hertwig, 1930–1933; Collin and Florentin, 1930, 1931; Monschau, 1930; Lindschau, 1933; Freerksen, 1933; Birkenmaier, 1934, a.o.), it may be assumed that under physiologic conditions the law of Heidenhain is of universal validity.

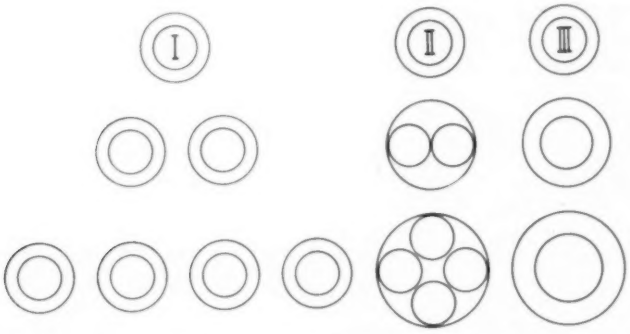

FIG. 1.—Nuclear sizes in mitosis (I), amitosis (II), and so-called "inner division" (III).

On account of the great significance of this discovery, it seemed desirable to extend these investigations to changes which may be included under the term *growth disturbances*, especially as Heiberg since 1907 has frequently stressed the observation that cells of malignant tumors are larger than those of their mother tissues. Measurements were started on normal and cancerous epithelium of tongues, the results of which have been published by my pupil Schmitz (1934). Then Arndt (1935) in our institute reported his findings in regeneration, adenoma and cancer of liver, and Epstein (1935) and Stapel (1935) the results they obtained in measuring cells of salivary glands and their tumors. To this I added data on lymphocytes, lymphoid hyperplasia and lymphosarcoma furnished by my coworkers Repsilber and Vorbeck (1935). Since then further measurements have been carried out by my pupils Carstens, van Hettinga, Kaiser, Kendziorra, Krause, Lohse, Mondry, Neuss, Pentz, Rentzow, Schreiber, Schwermer and Simon, the results of which are the subject of this paper.

Material and Method. The material of our study consists of 230 specimens, half of which were disturbances of growth. Eighty cases were tumors. As the usual methods of fixation and imbedding, especially imbedding in paraffin, lead to shrinkage of the cells up to 30 % and more (Ehrich and Cohn, 1931; G. Hertwig, 1931), only formalin fixed frozen sections (and in a few instances also sections imbedded in gelatine) were used. Jacobj's (1935) statement that it is sufficient to use methods of the same kind to get incontestable comparable data cannot be accepted, for the degree of shrinkage depends not only upon the kind of the fixative and imbedding, but also upon the time of application, the size of the specimens and other factors (Ehrich and Cohn).

For obvious reasons we had to content ourselves with measuring nuclei only. As the nuclear-cytoplasmic ratio of the cells of a given tissue can be regarded as constant, the conclusion may be drawn that the principles drawn from this study can be applied to whole cells too.

To obtain exact measurements, the nuclei, magnified 2500 times, were drawn on paper by means of Edinger's drawing projection apparatus. In every field were drawn all nuclei whose contours stood out clearly. The measurements were carried out by determination of the two largest diameters being perpendicular to each other. After conversion into mikra the volumes were calculated by the simple formula $V = r^3$ (r being $\frac{2d}{4}$), for we were interested in comparable values only.*

In most specimens 1000 nuclei were measured. The total number of nuclei measured amounts to about 220,000.

To find the sizes of the nuclei that are contained in a given tissue it is desirable to enter the values in a table (Table 1) or to plot a curve (Fig. 2). In doing so one obtains one or more peaks that represent the nuclear sizes searched for. As in most tissues two or more sizes are found, the most frequent one is called the *regular class* (Regelklasse, Jacobj). If the study of the regular class conceals other nuclear sizes, as can happen if there are only relatively few large cells in a tissue, one should make special measurements of a selected number of large cells. By this method of Jacobj in most cases the sizes of the larger nuclei can also be brought out.

TABLE 1.—NUCLEAR SIZES OF TONGUE EPITHELIUM. THIS SPECIMEN CONTAINS TWO NUCLEAR CLASSES THE VOLUMES OF WHICH ARE WITHIN A GEOMETRICAL LINE. THE LARGER NUCLEI BEING MORE FREQUENT THAN THE SMALLER ONES REPRESENT THE REGULAR CLASS.

Volumes of nuclei in r^3 . . .	22	26	30	34	39	45	51	52	64	71	80	88	97	107
Number of nuclei	40	60	*90*	70	60	40	70	80	*120*	100	90	70	60	50

* Only tissues with round nuclei were selected.

The Physiologic Range of the Nuclear Volumes. On reading the papers that have been published on the subject, the impression is gained that it is believed not only that the nuclear sizes of the same organ are constant in different individuals of the same species, but also that those of different organs in the same individual with

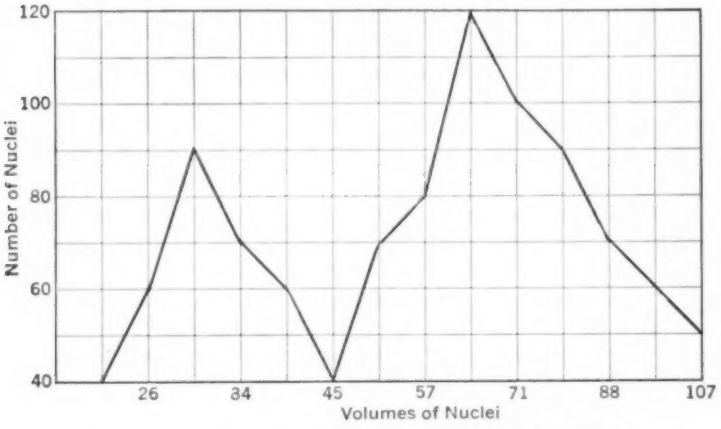

FIG. 2.—The figures shown in Table 1 presented in a curve.

TABLE 2.—VARIATIONS IN NUCLEAR SIZES IN MEN.

Cells.	No. of specimens studied.	Nuclear classes observed (regular class in Italics).	Size of regular class. Radius in μ.	Volume in r^3.
Epithelium of:				
Tongue	4	N_1 N_2 N_4	4.15–4.4	71.5–85.2
Tonsils	3	N_1 N_2 N_4	3.95	61.6
	9	N_1 N_2 N_4	2.95–3.45	25.7–41.1
Skin	3	N_1 N_2 N_4	2.9 –3.5	24.4–42.9
Mucous elements of salivary glands	8	N_1 N_2 N_4	2.9 –3.3	24.4–35.9
Serous elements of salivary glands	13	N_1 N_2	2.8 –3.1	22.0–29.8
Ducts of mucous glands	11	N_1 N_2 N_4	2.55–3.0	16.6–27.0
Ducts of serous glands	13	N_1 N_2 N_4	2.4 –2.9	13.8–24.4
Hypophysis	10	N_1 N_2 N_4	2.5 –2.9	15.6–24.4
Prostate	7	N_1 N_2	2.4 –2.9	13.8–24.4
Thyroid gland	4	N_1 N_2 N_4	2.45–2.6	14.7–17.6
Resting breast	9	N_1 N_2	2.1 –2.8	9.3–22.0
Puerperal breast	4	N_1 N_2	2.5 –2.9	15.6–24.4
Lymphocytes	33	N_4 N_2 N_1*	2.7 –1.9	19.7– 6.9

* Whereas most cells increase in size during growth, the lymphocytes as other blood cells decrease.

a few exceptions are in the same geometrical line. According to Jacobj (1935) here also exist great, unexpected correlations in that the typical nuclear volumes of different kinds of cells are, as he states, integer multiples of an elementary basal quantum. The reason that the anatomists reached this conclusion is probably because all of them studied only one or a very few organs of the

same kind. If they had studied series of organs, this opinion would not have arisen.

Concerning the first question, namely the *behavior of the nuclear volumes of the same organ in different individuals of the same species*, it can be seen from Table 2 that they are by no means constant. If we disregard the organs of which only 3 to 4 specimens have been measured, and if we disregard the lymphocytes which as we will see behave differently, we find variations of 30 to 80 % (in most cases about 44 to 56 %). The smallest variations were found in the parenchyma of salivary glands, the largest in breasts.

The factors that cause these variations appear to be manifold. A very important factor seems to be the *functional state* of the cells. If we look at the values of *resting breasts* (Table 3) we find that the nuclear volumes increase with increasing age, especially after the menopause, and that after the 65th year of age, which can be regarded as the point when old age begins, they decrease again. As these changes are not in the proportions of the law of growth, which are as has been stated in a geometrical line, *they cannot be an expression of genuine growth, but must be looked upon as changes of simple swelling and shrinkage*. The causes of these changes may be searched for in functional differences or in a changing control of the innersecretory organs. The shrinkage after the 65th year, however, is probably due to *atrophy of old age*.

Concerning the low nuclear sizes of our 21-year-old girl we may have to deal with a starting point of the swelling that increases with age. Whether this is true or not can be disclosed by further studies only.

If we turn now toward our *puerperal breasts* (Table 3), we easily recognize that the nuclei of all cases are much enlarged as compared with the resting breasts of the corresponding ages. As the enlargement amounts from 26 to about 100 %, we may conclude that also here we have not to deal with genuine growth but with simple swelling. The cause of this is certainly of functional or internal secretory character.

That the functional state of the cells is really an important factor in the variations of nuclear sizes is further illustrated by a comparison of the cyclicly functioning breasts with the steadily functioning *prostate*. If we look at Table 4 we find that after puberty the nuclear volumes of the prostate vary very little only. This constancy is in accord with the fact that the prostate is a gland that after puberty works very steadily. Before puberty we find much smaller nuclei. But as the difference amounts to 37 % only, these nuclei cannot belong to a smaller nuclear class. It rather must be suggested that the cells of the prostate during puberty undergo a swelling analogous to the swelling of breast tissue during functionally revolutionary times. This suggestion is in accord with the statement of Stieve, according to which the prostate develops very rapidly during puberty.

TABLE 3.—VARIATIONS IN NUCLEAR SIZES IN RESTING AND PUERPERAL BREASTS. (This table shows the regular class only.)

		RESTING BREASTS (No. of nuclei).																		PUERPERAL BREASTS (No. of nuclei).							
Age in years:		21.		35.		37.		42.		49.		54.		62.		64.		79.		22.		26.		36.		36.	
Radius in μ.	Volume in r^3.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
1.7	4.9	18	2	..	..	6	3	..	..	..	..	..	..	..	1	..	..	..	..	4								
1.9	6.9	*103*	14	2	5	11	17	1	1	9	1	4	1	2	3	..	..	2	..	23	..	3	..	..	..	5		
2.1	9.3	*199*	88	25	16	48	35	21	27	36	8	22	9	20	8	2	4	19	4	99	10	14	..	4	10	13	6	
2.3	12.2	69	*187*	81	59	92	86	64	58	80	44	58	25	40	53	27	22	81	44	*221*	46	38	2	30	15	23	24	
2.5	15,6	11	95	*157*	*127*	*126*	*109*	*125*	*108*	*115*	*113*	*109*	92	106	96	94	52	*149*	*134*	*254*	*146*	116	11	73	71	41	75	
2.7	19.7	1	11	*135*	*100*	*118*	97	*149*	*124*	*108*	*144*	*129*	*148*	*135*	*114*	*139*	84	*127*	*157*	169	*129*	*218*	37	*132*	*117*	*79*	96	
2.9	24.4	..	1	75	64	65	57	96	95	37	90	87	*130*	101	*139*	*123*	*110*	44	50	85	82	*274*	83	*120*	*116*	*84*	*124*	
3.1	29.8	..	..	22	21	26	16	36	45	6	24	54	79	59	90	69	87	11	14	37	32	*179*	94	90	84	*72*	*119*	
3.3	35.9	..	..	5	5	11	8	9	22	6	7	27	17	26	43	24	54	2	3	13	13	115	*96*	34	55	40	84	
3.5	42.9	..	..	..	1	3	1	1	6	1	2	5	2	8	27	6	23	..	..	3	4	50	*92*	8	24	28	38	
3.7	50.6	..	..	..	1	1	1	..	5	..	1	3	1	3	7	1	13	..	..	3	..	9	51	2	8	14	19	
3.9	59.3	..	..	..	..	..	1	..	2	..	..	..	..	..	3	..	1	..	..	..	..	4	23	..	..	6	7	
4.1	68.9	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	2	5	..	..	2	1	
4.3	79.5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	..	2	1	
4.5	91.1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4					

a = Acinus; b = Ductus lactiferus.

TABLE 4.—VARIATIONS IN NUCLEAR SIZES IN NORMAL PROSTATES.
(This table shows the regular class only.)

Radius in μ.	Volume in r^3.	Age in years. 14	17	18	35	49	52	59
		Number of nuclei.						
1.6	4.1	12	..	..	1	..	..	1
1.8	5.8	74	..	1	4	..	2	5
2.0	8.0	170	9	10	23	15	12	24
2.2	10.6	237	51	36	77	34	55	114
2.4	13.8	*283*	172	126	226	98	108	237
2.6	17.6	243	*351*	226	*324*	170	216	*312*
2.8	22.0	158	*314*	*319*	*305*	*216*	*241*	*306*
3.0	27.0	64	157	220	198	*249*	216	192
3.2	32.8	21	89	145	105	151	179	64
3.4	39.0	4	28	78	32	101	86	31
3.6	46.7	3	6	26	12	40	48	9
3.8	54.9	1	..	10	4	15	16	2
4.0	64.0	..	..	6	1	1	9	..
4.2	74.1	..	..	2	..	1	..	..
4.4	85.2	..	..	4	..	..	..	..

Whereas in breasts and prostates the factors that cause variations of the nuclear sizes appear to be mainly functional in character, in *salivary glands* other factors also seem to play an important rôle. One of these factors seems to be the *general state of nutrition* or the *kind of death*, for large nuclei were mainly found in large acini and these mainly in well-nourished persons that died suddenly, whereas emaciated persons that died slowly usually showed small acini as well as small nuclei. This finding is in accord with the general opinion that somatic glands are susceptible to atrophy whereas the genetic glands are resistant to a certain degree.

If we turn now to the *lymphocytes* we shall recognize that the much greater variations found in these cells are due to quite different causes. Table 5 shows that in the so-called germinal centers of the lymphatic tissue three nuclear classes occur, the volumes of which measuring V = 14.4 – 20.4, 27.7 – 36.8, and 52.8 – 65.4 r^3 are in the proportion of 1:2:4. Thus we have to deal with three sizes of lymphocytes that correspond to the small, medium-sized and large lymphocyte of the terminology of my earlier publications (1928, 1931). The regular class was that of the small lymphocytes in all our cases.

If we look now at the solid secondary nodules, pseudo-secondary nodules and lymphoid tissue we find indeed also here in most cases nuclear classes which measuring V = 25 – 27.6 and 51.7 – 66.1 r^3 correspond to the medium-sized and large lymphocytes of the germinal centers. But instead of small lymphocytes with the nuclear sizes of V = 14.4 – 20.4 r^3 we find in most cases lymphocytes the nuclear volumes of which show all transitions between V = 6.6 r^3 to V = 12.6 r^3. Thus we find sizes that not only are out of the proportions of the other lymphocytes but also show all transitions between the sizes of the small lymphocytes of the germinal centers and the next lower figure of the same geometrical line. If we com-

pare cases of corresponding ages only this fact comes out more distinctly still.

The significance of this finding seems to be clear. If we recall that in germinal centers abundant karyokinetic figures occur whereas in solid secondary nodules, pseudo-secondary nodules and lymphoid tissue these usually are scarce, we may conclude that, in contrast to the large, medium-sized and small lymphocytes of the germinal centers which certainly originate by mitosis, the smaller lymphocytes of the other lymphocellular tissues, that are out of this proportion, are formed by *shrinkage*.

The question why in most cases shrunken small lymphocytes but in some cases those that are not shrunken prevail, will not be discussed here. But it may be stated that the age of the individuals, the periodic occurrence of the lymphopoiesis and the rapidity of formation of lymphocytes probably are factors concerned.

Besides these distinct maxima, there are in a few instances figures that show no maxima at all but wide ridges that reach from the size of the large lymphocytes to that of the medium-sized lymphocytes or from the medium-sized lymphocytes to the small lymphocytes that are not shrunken or from these to the shrunken ones (Table 5). These ridges certainly are an expression of the suddenness by which the transformation of the lymphocyte occurs (Ehrich, 1931). This sudden transformation is a fine example of the rhythmic course of growth phenomena.

If we turn now towards the second question, namely to the *behavior of the nuclear volumes of different organs*, we find (Table 2) that also these show no conformity. If we compare nuclei of the same order we find sizes that show all transitions from $V = 9.3 - 22.0\ r^3$ to $V = 24.4 - 42.9\ r^3$. As these sizes differ by more than 100%, it can be concluded that in different organs nuclei of almost every size can be found.

The causes of this variation are far from being understood. If we recall however that in livers and salivary glands the volumes of the nuclei of the epithelial cells of the ducts and those of the parenchymal nuclei are in the proportion of 1:1.5 (Arndt, Epstein), it may be assumed that *functional differentiation* plays an important rôle.

From all these observations we may conclude that the assumption of the anatomists, according to which the nuclei of a given organ as well as of a given individual are of constant size or integer multiples of an elementary basal quantum, is not correct. In fact, there is *an immense variation not only in the same organ in different individuals of the same species but also in different organs of the same individual*. The factors that cause these variations seem to be manifold. In physiologic variation apparently functional influences play the main rôle.

TABLE 5.—VARIATIONS IN NUCLEAR SIZES OF THE LYMPHOCYTES OF SECONDARY NODULES AND LYMPHOID TISSUE.

(This table shows all maxima observed.)

	Age	Volume in r^3.			
		N_1.		N_2.	N_4.
Flemming's secondary nodules (germinal centers)	8 months	....	14.8	21.0–57.1	
	2 years	....	14.4	33.6	57.1
	4 "	....	17.2	35.1	
	15 "	....	12.6–36.5		56.0
	16 "	....	15.2	32.8	59.4
	16 "	....	18.2	33.6	58.3
	17 "	....	16.2	32.0	56.0
	19 "	....	15.6–31.3		52.8
	20 "	....	16.2	27.7	58.3
	24 "	....	20.2	33.5	
	24 "	....	20.2	36.8	65.4
	25 "	10.6–16.6		29.1	56.1
	30 "	10.6–16.6		30.5	56.1
	32 "	....	19.2	36.8	
	38 "	....	17.2	33.5	62.9
Solid secondary nodules	Newborn	9.6	....	28.0	
	"	10.3	....	27.7	
	"	12.2–16.6		28.0	
	"	11.0	....	28.1	
	"	....	14.3	29.1	56.0
	4 days	6.6			
	4 months	7.7	....	26.4	
	9 "	10.3	....	27.7	51.7
	7 years	8.3	....	26.4	
	17 "	12.6	....	34.4	58.3
	19 "	10.7			
	22 "	12.2–15.6		36.8	
	78 "	11.4–15.6		31.3	62.8
Pseudo secondary nodules	Newborn	11.0	....	25.0	
	4 days	8.5	....	25.0	
	4 months	11.0	....	30.5	51.7
	7 years	9.5	....	27.7	....
	22 "	13.0–15.6		33.5	53.8
Lymphoid tissue	1½ months	13.0–15.6		37.6	
	8 "	....	16.2	26.8	57.1
	1 year	....	14.8	32.8	
	2 years	12.2	....	30.6	
	16 "	....	15.7	30.6	
	17 "	11.8	....	32.1	
	19 "	....	15.2	36.8	
	22 "	11.8	....	29.8	64.0
	30 "	10.6	....	29.8	
	38 "	....	14.7		
	78 "	12.2–18.6		38.5	66.1

The Nuclear Volumes in Hypertrophy and Atrophy. About the nuclear volumes in hypertrophy and atrophy little is known. Data obtained by the variation statistical method are, as a matter of fact,

available in *hypertrophy of the liver* only. After Clara (1930) had made the observation that in compensatory hypertrophy of the liver, besides the usual nuclei of the sizes N_1, N_2 and N_4, the sizes N_8 and N_{16} also occur, Arndt (1935) was able to show that the hypertrophy in liver cirrhosis is also characterized by the fact that the number of the larger nuclei increases at the cost of that of the smaller ones. Whereas in a normal liver he found nuclei of the proportion

$N_1 = 70\,\%$, $N_2 = 19\,\%$, $N_4 = 11\,\%$

in two cirrhotic livers he found the proportion of about

$N_1 = 43\,\%$, $N_2 = 35\,\%$, $N_4 = 13\,\%$, $N_8 = 9\,\%$,

$N_1 = 38\,\%$, $= N_2 = 29\,\%$, $N_4 = 27\,\%$, $N_8 = 4\,\%$, $N_{16} = 2\,\%$

If we compare these data with findings we obtained in *hypertrophy of the prostate*, we find very similar relations. Whereas our normal prostates showed nuclei of the mean proportion of about

$N_1 = 83\,\%$, $N_2 = 17\,\%$

in our hypertrophic prostate we found the proportion of about

$N_1 = 30\,\%$, $N_2 = 68\,\%$, $N_4 = 2\,\%$

The only difference in Arndt's and our cases is one of degree. Whereas in his cases the number of the larger nuclei ($N_2 - N_{16}$) increased about 27 to 32 %, in our cases the increase amounted to 53 %. The cause of this difference becomes clear, if we consider that an excessive hypertrophy of the prostate, as in our case, represents a much higher degree of hypertrophy than the hypertrophy of the liver in liver cirrhosis.

Thus is can be stated *that in hypertrophy of certain organs cells occur, the nuclear sizes of which are integer multiples of the normal sizes, and the frequency of which is shifted from the smaller to the larger ones.* As all sizes found were within the proportions of Heidenhain's law of growth, we may *conclude that here we have to deal with a true disturbance of growth.*

That similar changes occur also in *atrophy* can be seen from a case of *atrophy of the thyroid gland.* Whereas four apparently normal glands showed nuclei of the mean proportion of about

$N_1 = 92\,\%$, $N_2 = 7\,\%$, $N_4 = 1\,\%$

a very atrophic gland showed that of about

$N_1 = 99\,\%$, $N_2 = 1\,\%$[1]

These figures show clearly that in atrophy of certain organs the reverse occurs of what we just have seen in hypertrophy.

In other cases of hypertrophy and atrophy, however, the outstanding features are changes that are of a quite different nature. If we regard the enlargement of the *breasts* during pregnancy described in the foregoing chapter as a functional hypertrophy and its diminution in old age as a senile atrophy, we can conclude *that in certain organs hypertrophy and atrophy is due at least in part to simple swelling and shrinkage of the cells.* This change, however, cannot be looked upon, as has been pointed out already (pp. 775–779),

[1] In this case also a shrinkage of the nuclei could be noted.

as a true growth disturbance, but rather should be called a functional or nutritional variation.

If we turn to the types of hypertrophy and atrophy that usually are called *hyperplasia* (numerical hypertrophy) and *numerical atrophy*, we again find different changes. The outstanding feature in these cases is an increase and decrease of the number of the cells, whereas a change of the size plays a minor rôle. If we compare the nuclear sizes we obtained in 3 cases of *lymphatic hyperplasia* (hyperplasia with the formation of so-called germinal centers) and in 6 cases of *lymphoid hyperplasia* (diffuse hyperplasia without secondary nodules) with those of normal germinal centers and lymphoid tissues (Table 6), we find a close concordance. Concerning the frequency of the three nuclear classes a shift from the small lymphocytes to the larger ones could not be detected in lymphoid hyperplasia. In lymphatic hyperplasia, however, we observed a definite increase of the number of the medium-sized lymphocytes at the cost of the small ones, which in one case even led to a prevalence of the medium-sized lymphocytes. From these findings the conclusions may be drawn, *that in hyperplasia we have to deal with an increase in the number of cells mainly, but that in certain cases there occurs also a shift from the smaller to the larger cells, similar to the shift that has been observed in hypertrophy of the liver and prostate.*

TABLE 6.—THE NUCLEAR SIZES OF LYMPHOCYTES IN LYMPHATIC AND LYMPHOID HYPERPLASIA.

	No. of specimens.	Volumes of nuclear classes.		
		N_1.	N_2.	N_4.
Flemming's secondary nodules:				
Normal	15	14.4–20.2	27.7–36.8	52.8–65.4
Lymphatic hyperplasia	3	14.7–16.6	27.7–31.3	57.1
Lymphoid tissue:				
Normal	11	10.6–12.2		
		14.7–16.2	29.8–38.5	57.1–66.1
Lymphoid hyperplasia	7	9.3–12.2		
		14.7–16.2	27.0–31.3	

Specimens of *numerical atrophy* have so far not been studied. But there can be no doubt that it is characterized by a decrease in the number of cells.

From all these observations it can be seen that there are several avenues by which hypertrophy and atrophy can arise. In some cases we have to deal with true growth disturbances (increase or decrease in size or number of cells in the proportion of Heidenhain's law of growth) and in others with changes that should be headed by the term of functional or nutritional variations (simple swelling or shrinkage of cells outside of these proportions). In many cases two of these three avenues are chosen, one overlapping the other.

The question why in some cases the one and in others another avenue is chosen, can be answered in part at least. As hyperplasia

and numerical atrophy are found in tissues only that show a great regeneratory ability (tissues with unstable elements (Levi)), whereas the others are observed in tissues with little or no regeneratory ability (tissues with stable or imperishable elements (Levi)), there can be no doubt that regeneratory ability or its cause is one of the factors concerned. The question however as to why the increase and decrease of the size of the cells in some cases is due to true changes of growth and in others to simple swelling and shrinkage, cannot be answered with certainty. But as the former has been observed only in tissues, the nuclear sizes of which as well as their function appear to be very steady, whereas the latter was found in glands the nuclear sizes of which as well as their function show great periodical changes, it suggests itself that it is the steadiness, or the functional variability which plays the deciding rôle. Whereas organs which react even normally with swelling and shrinkage of their cells will do so also in pathologic conditions; organs which have no such abilities can react only with a new growth within the proportion of Heidenhain's law of growth.

In summary we may conclude therefore that *hypertrophy and atrophy can be due to a change in size or number of the cells in the proportions of Heidenhain's law of growth (true growth disturbances) or to a simple swelling or shrinkage (functional or nutritional variations). Which of the avenues is chosen, depends largely upon the regenerative ability of the tissues and probably upon the varying ability of functional swelling or shrinkage of their cells.*

The Nuclear Volumes in Benign Tumors. In many papers it has been stated that the nuclei of benign tumors are larger than those of their mother tissues. Reliable data however are scarce. Also, as Arndt (1935) has pointed out, the figures given by Heiberg do not stand adverse criticism.

The first to study the nuclei of benign tumors by means of Jacobj's method was Arndt (1935) in our institute. He found that the single nuclear classes of liver adenomas were to be sure in the proportion of Heidenhain's law of growth, but that they were distinctly larger—the enlargement amounting to about 25%. Then my pupil Stapel (1935), who measured several tumors of salivary glands, reported that the nuclei of the so-called mixed tumors, which, according to our view, must be looked upon as adenomas of the serous elements of the salivary glands were about 20 to 25% larger than those of their mother cells.

In the meantime we have studied some more benign tumors (see Table 7). From this table it can be seen that papillomas of the skin as well as cystic tumors and fibroadenomas of the breast consist of cells, the nuclei of which are bigger than those of their mother cells. As the latter vary a great deal, exact figures for the increase cannot be given. But it is beyond doubt that in these tumors also the increase does not exceed 50%. As these figures do not reach

the proportions of Heidenhain's law of growth (figures of a geometrical line), we can conclude *that the enlargement of the nuclei of benign tumors is not due to true growth but rather to a simple swelling, analogous to the simple swelling observed in hypertrophy.* This conclusion is not contradictory to the fact that benign tumors as a whole are growth disturbances, for their outstanding feature certainly is an increase in the number of their cells.

TABLE 7.—NUCLEAR SIZES IN BENIGN TUMORS.

	Measurements made by:	No. of specimens studied	Nuclear class observed (regular class in Italics).	Size of regular class, volume in r^3.
Epithelia of skin	Kaiser	3	N_1 N_2 N_4	24.4–42.9
Papilloma of skin	Kaiser	1	N_1 N_2 N_4	51.7
Serous epithelia of salivary glands	Epstein	13	N_1 N_2 (?)	22.0–29.8
So-called "mixed tumor" of parotid	Stapel	4	N_1 N_2 N_4	29.8–32.8
Epithelia of liver parenchyma	Arndt	4	N_1 N_2 N_4	28.4–37.6
Liver cell adenoma	Arndt	4	N_1 N_2 N_4	34.3–46.7
Epithelia of resting breast	van Hettinga	9	N_1 N_2	9.3–22.0
Epithelia of puerperal breast	van Hettinga	4	N_1 N_2	15.6–24.4
Cystic breast	Pentz	4	N_1 N_2	20.3–30.6
Fibroadenoma of breast	Pentz	4	N_1 N_2	20.3–27.9

The cause of the swelling of the nuclei in benign tumors cannot as yet be detected. That we have not to deal with functional factors, as in hypertrophy, seems to be clear. If the assumption of Wermel and his associates (1932–1934) is correct, *i. e.*, that the swelling of nuclei in tissue cultures is due to the loss of control by the whole organism, then the idea is suggested that in benign tumors we might have to deal with cells that are excluded from this control. But whether this is true or not must be left to further studies.

The Nuclear Volumes in Malignant Tumors. It has been stated frequently that the cells of malignant tumors are larger than those of their mother tissues. Especially Heiberg has stressed this point again and again (1907–1935). Whereas in earlier communications he merely stated this finding, in later publications he attached a profound significance to it, namely, that this was due to tetraploidy, *i. e.*, doubling the number of chromosomes, and that this tetraploidy was the cause of the greater energy of growth of malignant tumors. If these papers have not found the echo they deserved, this was certainly due to the rather unreliable method Heiberg used. Had he used the variation statistical method, cancer research perhaps would have taken quite another course in the last 20 years.

The first who used the variation statistical method in measuring the nuclei of malignant tumors was my pupil Schmitz (1930). He found that in carcinoma of the tongue *all* nuclei were *doubled* or

quadrupled in size, so that we felt we were entitled to speak of a change to another level of size not merely of cells but of the *whole epithelial tissue*. Then Arndt (1935) in our institute reported the same findings in carcinomas of the liver, whereas my pupil Stapel (1935), who measured tumors of the parotid gland, was even able to show that by this method a differential diagnosis between carcinomas of the acinar cells and of the ducts could be made. Finally I (1935) reported that measurements of lymphosarcomas gave results in full accord with those of carcinomas.

Schairer (1935), the only author who has since taken up these investigations, using the variation statistical method, was not successful because he used material differently fixed and imbedded, and because he overlooked the physiologic range of normal nuclear sizes. Therefore his statements need not be discussed here.

Since our preliminary reports we have measured many more malignant tumors. In the case of the sarcomas—with the exception of our lymphosarcomas, which I have discussed already (1935)—the mother cells could not be made out; therefore only our carcinomas will be considered here (see Table 8). It may be emphasized that these data are not selected but comprise *all* carcinomas measured by us.

TABLE 8.—NUCLEAR SIZES IN MALIGNANT TUMORS.

	Measurements made by:	No. of specimens studied	Nuclear classes observed (regular class in Italics)	Size of regular class volume in r^3.
Epithelium of skin	Kaiser	3	N_3 N_4 N_5	24.4–42.9
Cancer of skin	Kaiser	4	N_4 N_5 N_6	64.7–95.8
Basalioma of skin	Kaiser	2	N_4 N_5 N_6	40.2–42.0
Cancer of lip	Lohse	1	N_3 N_4 N_5	83.7
Malignant papilloma of anal region	Lohse	1	N_4 N_5	95.8
Epithelium of tongue	Schmitz	4	N_3 N_4 N_5	71.5–85.2
Cancer of tongue	Schmitz	4	N_4 N_5 N_6	140.2–192.2
Cancer of tongue	Schmitz	1	(?) N_6 N_{16}	344.3
Epithelium of tonsils	Schreiber	9	N_3 N_4 N_5	25.7–41.1
Epithelium of tonsils	Schreiber	3	N_3 N_4 N_5	61.6
Cancer of tonsils	Kendziorra	2	N_4 N_5 N_6 N_{16}	59.3–66.4
Serous epithelium of salivary glands	Epstein	13	N_3 N_4 (?)	22.0–29.8
Papillary cancer of salivary glands	Stapel	1	N_4 N_5 N_6	53.8
Epithelium of salivary gland duct	Epstein	13	N_3 N_4 N_5	13.8–24.4
Adenocarcinoma of gland duct	Stapel	4	N_4 N_5 N_6	35.9–42.0
Epithelium of liver parenchyma	Arndt	4	N_3 N_4 N_5	28.4–37.6
Cancer of liver parenchyma	Arndt	3	N_4 N_5 N_6	61.6–71.5
Epithelium of prostate*	Deysing	6	N_3 N_4	17.6–24.4
Cancer of prostate	Deysing	1	N_4 N_5	40.2
Cancer of prostate	Deysing	1	N_5 N_6	116.1
Epithelium of resting breast	van Hettinga	9	N_3 N_4	9.3–22.0
Epithelium of puerperal breast	van Hettinga	4	N_3 N_4	15.6–24.4
Solid carcinoma of breast	Drücke	2	N_4 N_5	36.8–43.9
Solid carcinoma of breast	Drücke	1	N_5 N_6	70.3
Adenocarcinoma of breast	Drücke	1	N_4 N_5	40.4
Scirrhus carcinoma of breast	Drücke	2	N_4 N_5	40.4–47.8
Scirrhus carcinoma of breast	Drücke	1	N_5 N_6	92.7
Scirrhus carcinoma of breast	Drücke	2	N_4 N_5	27.9

* One case before puberty left out (see Table 4.)

Looking over Table 8 we easily discern that, with the exception of our basal-cell carcinomas of the skin and of 2 of our cases of scirrhus of the breast, all our carcinomas show nuclear sizes that differ from those of their mother cells by the fact that they are doubled (in 30 cases) or quadrupled (in 4 cases). This comes out particularly well if we compare the sizes of the regular classes. As in no tumor nuclei were found the sizes of which corresponded to those of the lowest nuclear class of the other tissues, we can state that we are not entitled to speak of a simple shifting as observed in hypertrophy, but that we must speak of a *fundamental change to another level of size* —the levels being figures of a geometrical line.

Concerning our exceptions, it can be easily seen that the nuclei of our basal-cell carcinomas are also of double size, if we compare them not with the regular class of the skin epithelium but with the basal cells from which these tumors are derived. In our 2 exceptional cases of scirrhus of the breast, however, the nuclei are actually only 50% larger than those of their mother cells. But if we consider that in a scirrhus we have to deal with a tumor that is composed to a large extent of a very dense and firm connective tissue, which physically counteracts the expansion of the single tumor cells, then we safely can conclude that also these cases are no true exceptions, but variations due to the particular properties of scirrhus.

We can state therefore that malignant tumors are characterized by doubling or quadrupling of the sizes of their nuclei. A greater variability in the sizes of the individual cells certainly plays an important rôle too, the essential difference however is the turn into a higher level of size—a doubling or quadrupling.

The question whether the reverse is also true, namely, that doubling or quadrupling is characteristic of malignant growth, must be answered in the negative, however, since in a case of puerperal breast and benign goiter we found a similar change. But whereas in hypertrophy we had to deal with a *gradual* swelling or shifting of the cells, in cancer we have a *sudden turn*, a *jump into a higher level with no transitions whatever.*

Concerning the *pathogenesis* of the malignant cells no satisfactory explanation can be given yet. But since it is well known that the size of the nuclei with the exception of the functional or nutritional variations largely depends upon the quantity of chromosomes (Boveri, 1914; Jacobj, 1926; G. Hertwig, 1930–1932), it seems to be certain that this question and with that the question of carcinoma is a chromosomal one.

If we have two cells the one of which is double the size of the other, this doubling can be due to a double number or to a double size of the chromosomes. In the first case we speak of polyploidy, in the latter of polymery.

Whereas in normal germ cells polyploidy as well as polymery are said to occur (G. Hertwig), in normal somatic cells polyploidy has

not been demonstrated yet. Therefore the larger cells of the geometrical lines, which arise by "inner division," are supposed to be polymer in character (Jacobj).

The question whether polymer cells under normal conditions can divide again by mitosis, cannot be answered yet with certainty. In careful studies of regeneration of the liver Clara (1931) found mitoses almost exclusively in the smallest cells of the periphery of the lobules, which probably are monomer in character; in the very few larger cells that showed mitoses he found approximately the double number of chromosomes; but as his animals were poisoned by phosphorus, the possibility cannot be excluded that these cells had arisen by fusion, instead of by inner division, especially since he found other abnormalities of mitoses (see Politzer, 1934).

Also the occurrence of the so-called multiple succedan divisions, which lead to a reduction in size and which are best observed in germ and blood cells, does not help to solve this question; for in the case of germ cells we have to deal with heterotypic mitoses, whereas in blood cells satisfactory chromosome studies are not available. It may be mentioned in this connection that in leukemia haploid mitoses have been observed (Isaacs, 1930; Groat, 1933).

Concerning the chromosomes in malignant tumors many data are available. The principle findings, that have been confirmed again and again are diploid, tetraploid, octoploid, and even higher polyploid mitoses often in one tumor (Winge, 1927, 1930); Heiberg and Kemp, 1929; Lewis and Lockwood, 1929; Levine, 1929, 1931; Goldschmidt and Fischer, 1930; Hirschfeld and Klee-Rawidowicz, 1930; Andres, 1932; Alexenko and Natansohn, 1933). But as no data have been accumulated correlating the number of chromosomes to the size of the nuclei, and as no chromosomal measurements have been published, so that we do not know whether the chromosomes were monomer or polymer in character, no conclusions as to the significance of these findings can be drawn. It might be that Winge (1927) and Jacobj (1929) are correct when they assume that it is a heterotypic mitosis that starts malignant growth. Or it might be that Arndt (1935) is correct, who believes that polymer cells normally do not divide by mitosis, but that if they do, then cancerous cells develop. Especially the latter theory is very tempting, of course, but it cannot be excluded yet that a polymer cell cannot normally divide by mitosis. According to our present knowledge, therefore, we only can state that it seems to be established that the pathogenesis of the malignant cells is a chromosomal question, and that probably we have to deal with a derailing from the normal track of growth during mitosis or inner division.

Concerning the *etiology* of malignant tumors no new information can be expected by these studies. But attention may be paid to the fact that almost all agents that produce cancer are known also to produce chromosomal disturbances and *vice versa*.

In conclusion, therefore, we can say that *malignant growth is characterized by cells that are double or fourfold the size of their mother cells, and that this doubling or quadrupling probably is due to a derailing from the normal track of growth probably during cell division. The malignant cell, therefore, is a special cell and not an embryologic cell, for these belong to the smallest cells observed.* But if the malignant cell is a special cell and if its specialty is its double or fourfold size, then we safely can conclude that *the double or quadruple size of the malignant tumor cells is an anatomical expression of the anaplasia or kataplasia of malignant tumors so long searched for.*

Summary. The present report is based upon the measures of 220,000 nuclei of 230 specimens, half of which were growth disturbances.

In all tissues studied, normal as well as pathologic, several nuclear classes were found the sizes of which were in the proportions of Heidenhain's law of growth.

The nuclear sizes of *normal tissues* are by no means constant; they vary not only in the same organ in different individuals, but also in different organs of the same individual. In physiologic variations apparently functional influences play the main rôle.

In *hypertrophy* and *atrophy* several mechanisms are involved. In certain organs we find an increase or decrease in the size of the nuclei in the proportions of Heidenhain's law with a shift from the number of the smaller to the larger cells or *vice versa* (liver, prostate). In other organs we merely observe an increase or decrease in the number of cells with or without change of their size (lymphatic and lymphoid tissue). In still others we mainly find a simple swelling or shrinkage outside of the proportions of Heidenhain's law (breast, thyroid). Which of these avenues is chosen depends largely upon the regeneratory ability of the tissues and probably upon the ability of functional swelling or shrinkage of their cells.

Benign tumors are characterized by cells larger than their mother cells. The enlargement is due to simple swelling and not to true growth.

Malignant tumors are characterized by cells which are double or fourfold the size of their mother cells, and which probably arise by derailing from the normal track of growth during cell division. The malignant tumor cell is not an embryologic cell, but a special cell that occurs in malignant tumors only. The double or quadruple size of these cells is an anatomical expression of the anaplasia or kataplasia of malignant tumors so long searched for.

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THE MECHANISM OF INACTIVATION OF MERCURIAL ANTISEPTICS BY SERUM, AND ITS IMPLICATIONS REGARDING THE POSSIBILITY OF INTRAVENOUS ANTISEPSIS.

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The hope of achieving direct chemical destruction of bacteria within the humors of their hosts has fascinated bacteriologists since the beginning of the science. So compelling indeed has this hope been that its realization has been sought at times immediately and empirically with too little consideration of the determining conditions involved. That the result has been disappointing should not occasion surprise.

The present investigation began with the attempt to prepare a serum-mercurial compound suitable for intravenous antisepsis. The failure of our therapeutic experiments, like those of Birkhaug and others,[1] compelled analysis of the chemical system comprising germicide, bacteria and serum.

A method has been developed for quantitative comparison of the bactericidal action of antiseptics, under various conditions.

This has permitted determination of the relative velocities of reaction between bacteria and mercurial and between serum and mercurial, the magnitude of the effect of serum on bactericidal action, and the type of reaction between mercurials and serum.

Comparison of the equivalent bactericidal action of various mercurials on bacteria suspended in 80% serum and in saline solutions has shown that from 300 to 1400 times the concentration of mercurial is required to exert equivalent bactericidal action in the presence of serum. Combination between serum and antiseptic has usually been assumed to occur, but had never been rigorously investigated. When a method of purifying such compounds was devised, they were found to be non-ionic and devoid of bactericidal action.

Methods and Materials. *Quantitative Method for Comparing the Bactericidal Power of Disinfectants.* The usual modifications of the Rideal-Walker method were unsatisfactory for our purpose as they depend on determining a point in concentration and time when no organisms survive. For the sake of comparison it was necessary to know the percentage surviving at any time. Plating experiments were essential for this purpose. For this reason a more accurate method of plating the organisms used was necessary. This allowed a closer mathematical approximation of the effect of serum on the antiseptic used.

The culture used was a smooth, non-motile, laboratory strain of *Eberthella typhosa* (0 901)[2] grown for 18 hours in extract broth at an initial pH of 7.0. It was centrifuged and resuspended in normal saline at a pH which was carefully adjusted to the first visible change of phenol red (pH 6.8). A slight deviation in the degree of acidity will kill many organisms in the time required to complete the experiment. Dilutions of the disinfectants were made with volumetric flasks and pipettes which had been carefully calibrated. The culture was successively diluted so that control plates showed about 500 colonies. This was a dilution of about 1:10,000 of the original culture. This number of colonies approximated a true statistical picture and was not too large to make counting of the total number of colonies on the plate tedious. That the number of organisms in the suspension on which the antiseptic is allowed to act is of importance can be seen in Fig. 1. Where the number of organisms is increased from 150 to 680, there is an increase in the killing time. Therefore, when comparing the activity of any antiseptics, the number of organisms in the suspension must be rigidly controlled.

Normal horse serum of the same lot was used throughout all the experiments. This is essential as it has been found that the effect of normal rabbit serum and of immune horse serum on bactericidal action of an antiseptic is appreciably different from that of normal horse serum. Meat-extract agar at a pH of 7.0 was used in doing all of the plating. Equal volumes of the suspension of the organisms in saline and the solution of the antiseptic being investigated were allowed to stand at room temperature. The solution of the antiseptic was twice the concentration being investigated to allow for the dilution with the suspension of bacteria. At predetermined intervals 0.2 cc. of the mixture was introduced into 10 cc. of broth, thoroughly mixed by shaking, and then 0.5 cc. of the broth dilution was placed in a Petri dish. After 10 cc. of agar was added, the plate was carefully rotated to insure thorough mixing.

When the effect of serum on antiseptic action was being investigated, 0.2 cc. of the suspension of the organisms was mixed with 1.6 cc. of serum

and 0.2 cc. of a solution of the antiseptic added. The antiseptic was ten times the concentration being investigated in order to allow for the dilution. This gave a concentration of 80% serum. Samples (0.2 cc.) were withdrawn at predetermined intervals, diluted in broth, and plated in the usual manner. This method of plating diluted any excess antiseptic a thousandfold, which is far beyond the killing range of the concentration of the antiseptics studied. All plates were counted after an interval of 4 days in the incubator at 37° C.

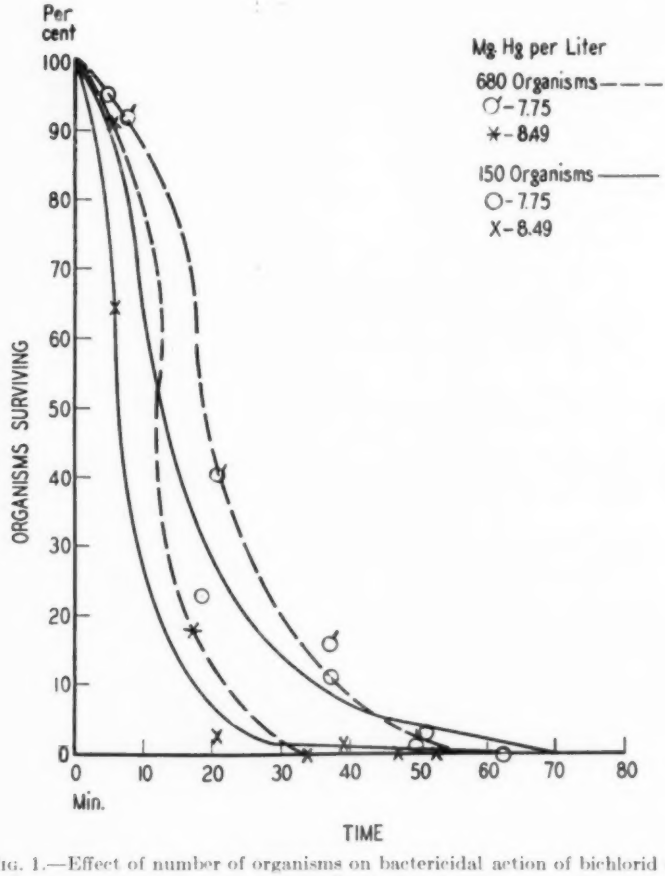

FIG. 1.—Effect of number of organisms on bactericidal action of bichlorid of mercury in serum.

Curves are then made in which the number of surviving colonies are expressed as percentage of the controls for various concentrations of the antiseptic. These percentages are plotted against time (Figs. 2 to 9 incl.). From points on these survival curves graphs are made representing the time and concentration at which various percentages of the organisms survive in different dilutions of the antiseptic, each line representing the same percentage of survivors (Figs. 10 and 11). They show the effect of the concentration on the killing power of the antiseptics studied. As any of

the curves representing per cent survival of the organisms at various times and concentrations form a straight line, a comparison of the antiseptics can be made, using any point on these curves. The 50% survival curve appears to give the best basis for comparison from the standpoint of statistical accuracy. A comparison of the 50% survival concentration at any desired time can be read from the curve. The selection of such a specific time will depend on the rate of activity of the class of antiseptics studied. This type of comparison is much more satisfactory than a mere inspection

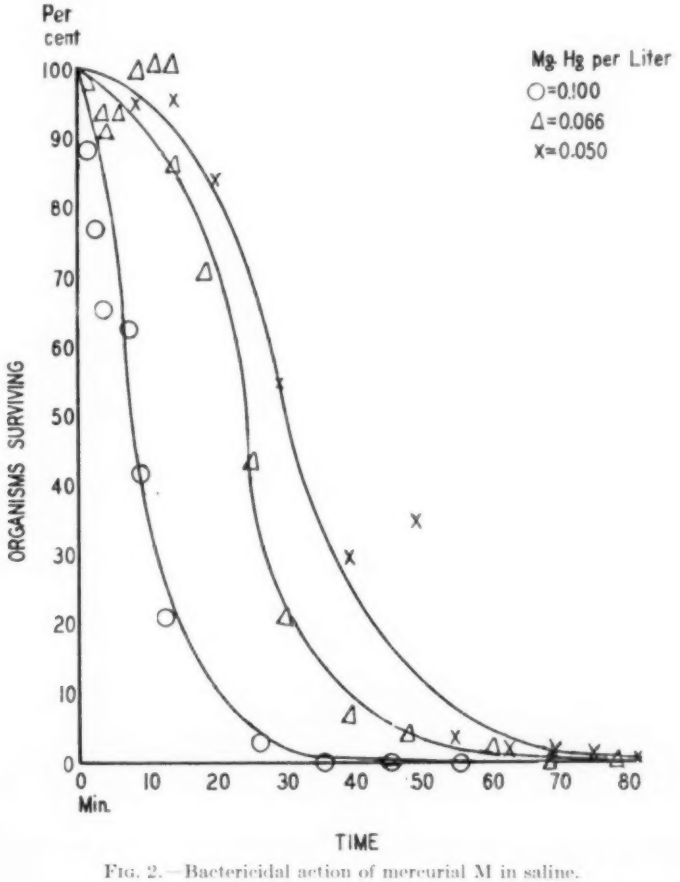

FIG. 2.—Bactericidal action of mercurial M in saline.

of time-survivorship curves of any antiseptics, as the latter are not usually superposable.

The accuracy of the above method as determined by the colony counts of plates made under identical conditions is approximately 10%. By this method it had been possible to construct and compare curves with sufficient accuracy to study: 1, the effect of the number of organisms on the position of the time concentration curves; 2, the relative speeds of reaction between bacteria and various mercurials; 3, the magnitude of the effect of serum on bactericidal action; 4, the type of reaction between mercurials and serum.

(Evidence has been obtained showing this to be an addition reaction, and not an adsorption reaction.)

Mercurials. Metaphen, Mercurial M, Merthiolate and Mercurochrome were not known to be chemical entities, so they were analyzed for mercury, and all figures are based on their mercury content. Mercuric chlorid (Merck reagent) was used, for comparison, since the chlorid ion is known to be non-toxic. Mercurochrome was obtained from Hynson, Westcott

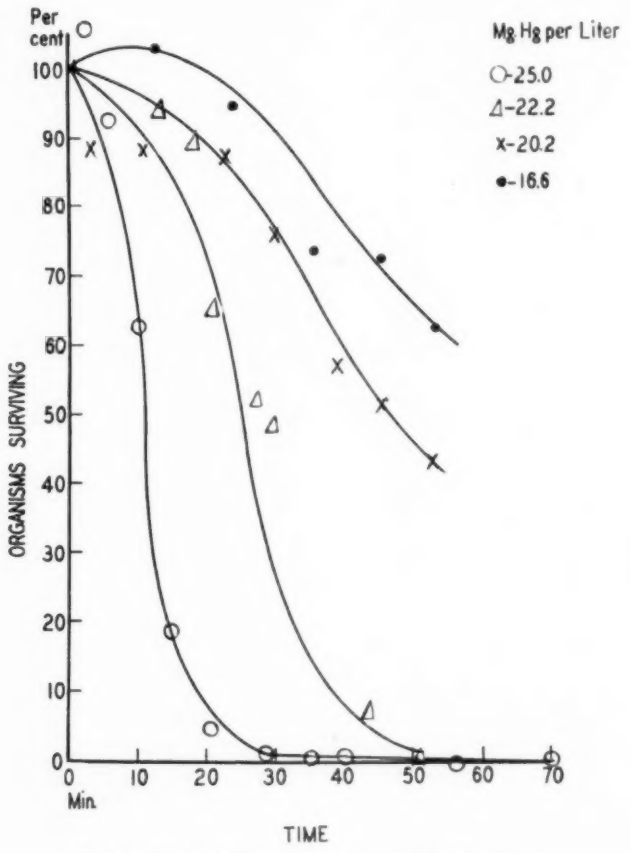

FIG. 3.—Bactericidal action of mercurial M in serum.

and Dunning. Merthiolate came from Eli Lilly and Company, and was marked "Released for use as a biological preservative." In some of the experiments a solution of Metaphen, 1:500, from the Dermatological Research Laboratories was used. Since we were unable to obtain any Metaphen powder from them when we began this investigation, Dr. A. Proskouriakoff* very kindly synthesized for us a mercurated nitro-ortho-

* We wish to thank Dr. Proskouriakoff not only for the compound but for giving us the benefit of his long experience with the chemistry of mercurials on the occasions when we asked his advice.

cresol in the laboratory at Jefferson Hospital. This will be designated Mercurial M for convenience. In our hands this behaved like Metaphen both in respect to chemical reactions and bactericidal activity, within the limits of experimental error. As experiments with Mercurial M and Metaphen are very similar, only Mercurial M will be reported.

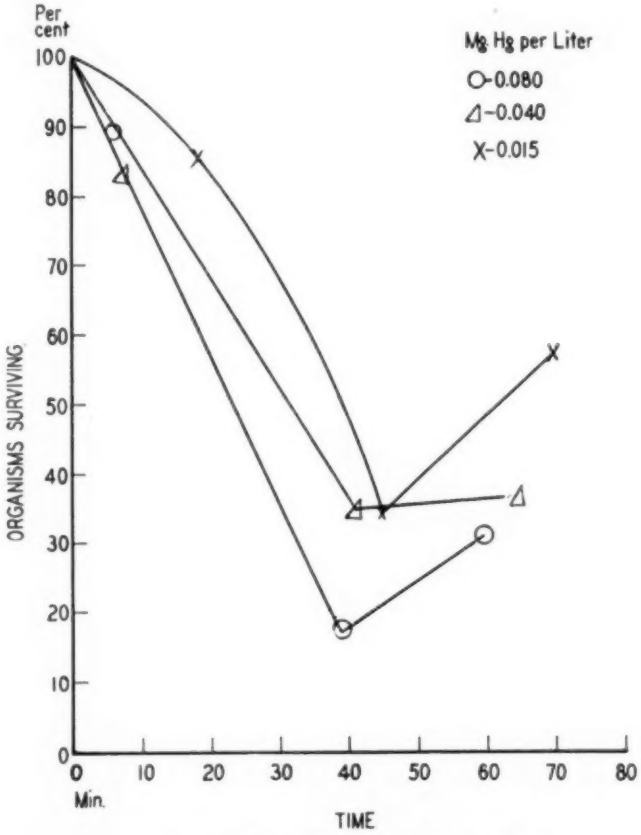

FIG. 4.—Bactericidal action of merthiolate in saline.

Serum. One lot of pooled normal horse serum obtained from Sharp & Dohme, at Glenolden, was used throughout the experiments. Due to the necessity of water as a solvent of the mercurials, only a concentration of 80% serum could be used in the plating experiments.

Temperature. All of the reactions were allowed to take place at laboratory temperature. The slight fluctuations in temperature were not of sufficient importance to be taken into account.

Results. 1. *Relation Between Antiseptic Action and Time and Concentration.* In Figures 2 to 9 we have plotted curves showing the effect of time and concentration on the bactericidal action of 4 of the mercurials studied, in saline and in serum. The concen-

tration has been plotted in milligrams of mercury per liter. Concentrations necessary to kill 50% of the organisms in 30 minutes can be compared to show the relative value of the antiseptics. Figure 2 shows that there is a rapid falling off in the efficacy of Mercurial M with a decrease in concentration, but even so, 50% of the organisms are killed in a dilution of 1 in 6,000,000 in 30 minutes.*

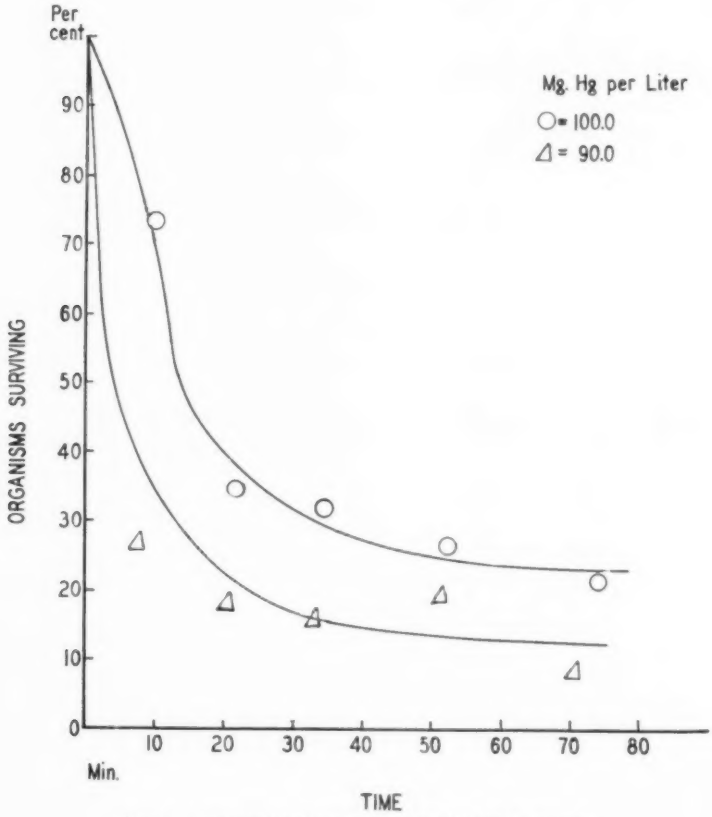

FIG. 5.—Bactericidal action of merthiolate in serum.

To produce this same effect in the same time in serum (Fig. 3), a concentration of 1 in 17,000 is required. This is a difference in concentration of approximately 340 times. A comparison of the time and concentration at which any certain per cent of organisms survive can readily be made by an inspection of survival curves derived from time-concentration curves (Figs. 2 to 9). Such survival levels for Mercurial M in saline and in serum are shown in

* A similar curve is obtained for Metaphen.

Figures 10 and 11. The 50% survival level curve is derived by plotting points representing the time at which 50% of the organisms survive for each concentration used, the slope of the line being determined by the time required for each concentration of the antiseptic to exert its effect. The other survival levels are determined in the same manner. With the aid of these curves, the time and concentration at which any per cent of the control organisms survive can be observed.

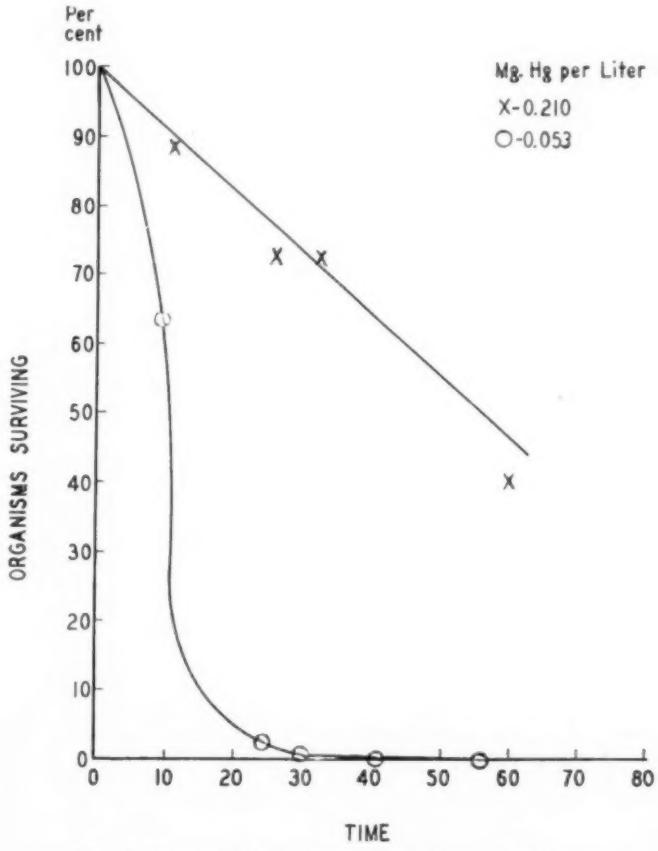

FIG. 6.—Bactericidal action of mercurochrome in saline.

Points on each survival level represent the same degree of reaction between a mercurial and bacteria, or between a mercurial and bacteria plus serum, for different times and concentrations. Curves drawn through such points represent the relationship between time and concentration for the same degree of reaction. As these survival levels form straight lines, the time of reaction is inversely

proportional to the concentration for any survival level, and therefore these reactions are addition reactions of the first order, and not adsorption reactions. In the latter case the lines would tend to be curved, and would represent reactions of a zero order. As it has been shown that the reactions between a mercurial and bacteria and between a mercurial and bacteria plus serum are strictly chemical addition reactions, the data concerning such reactions can

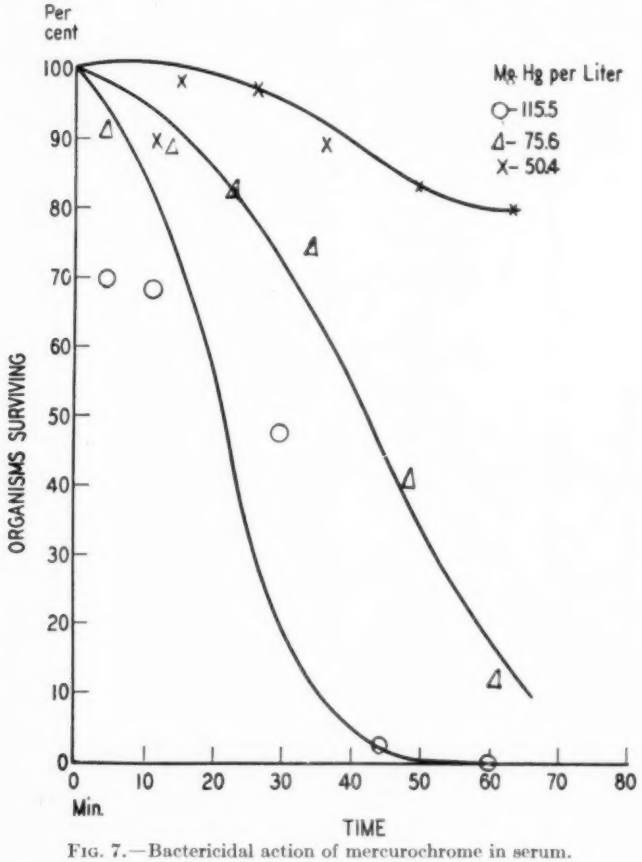

FIG. 7.—Bactericidal action of mercurochrome in serum.

be treated as such, and analyzed from a mathematical viewpoint. Thus survival levels can be considered as vectors of a degree of reaction. The different survival level curves for the reactions of bacteria with Mercurial M in saline are almost parallel, indicating the same relationship as to time and concentration for each survival level. When the time-concentration relationship is the same for each degree of reaction only one reaction is taking place, as no two reactions take place at exactly the same rate.

The survival levels showing the reactions of Mercurial M with bacteria in serum (Fig. 11) are not parallel, indicating two different reactions of different rates, which are going on simultaneously. As the additional component of this system is serum, the second reaction going on is between the mercurial and serum. From Figures 10 and 11 it can be seen that much more of the mercurial as mercury

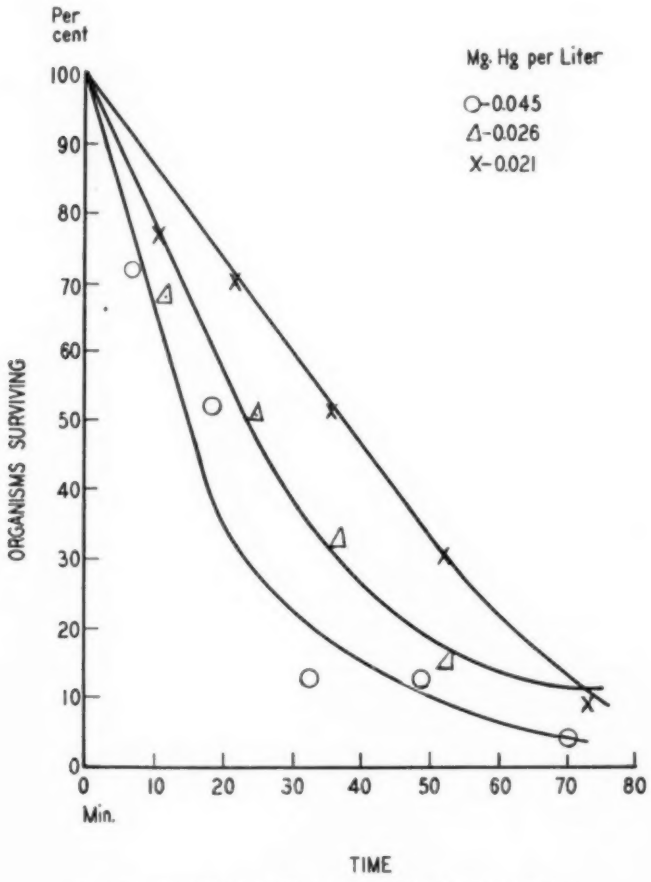

FIG. 8.—Bactericidal action of mercuric chlorid in saline.

is required to kill 50% of the standard suspension of organisms in the presence of serum than is required to kill 50% of the organisms in saline in the same time. It is evident from this that the reaction between serum and the mercurial is the faster, the serum being present in the larger amount. Whereas 0.07 mg. of Mercurial M as mercury is required to kill 50% of the suspension in saline in 20 minutes (Fig. 10), 24 mg. of Mercurial M as mercury are required

to kill the same number of organisms in the serum in the same time. Thus 24 — 0.07 mg. of Mercurial M are being inactivated for each 0.07 mg. of Mercurial M combining with the standard suspension of bacteria. About 340 molecules of Mercurial M are being inactivated by the serum for every one combining with the bacteria in this concentration of Mercurial M. All of the mercurials

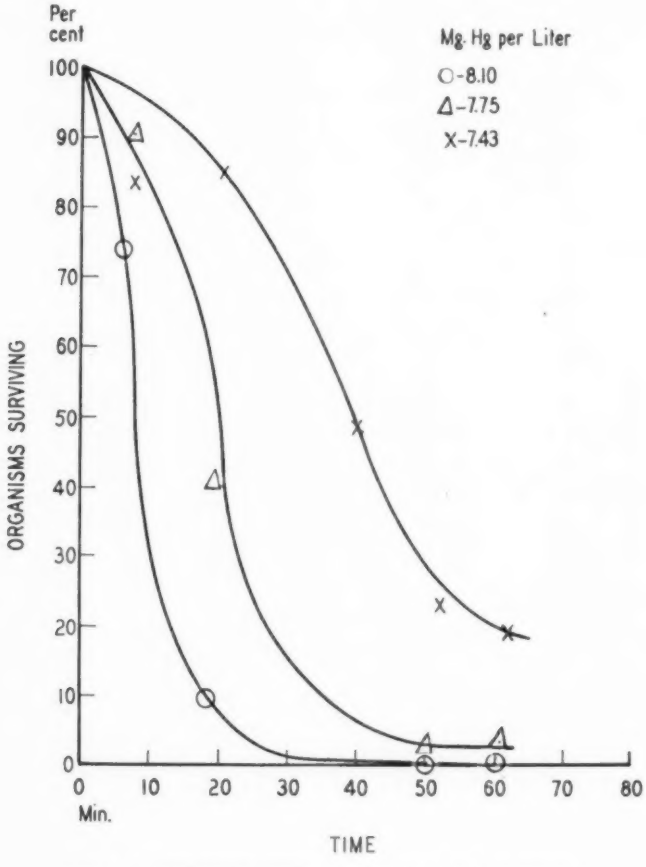

FIG. 9.—Bactericidal action of mercuric chlorid in serum.

studied show this tendency to be inactivated by serum, Mercurial M being given as an example. Where any of these mercurials is tested in the presence of a homologous immune serum, there is a still greater tendency toward inactivation of the antiseptic.

2. *The Relative Efficiency of the Mercurials Studied.* The survival level curves in serum (Fig. 11) indicate that there is a rapid falling off in the efficiency of Mercurial M with time. Thus, if

Mercurial M were to be given as an intravenous antiseptic, sufficient amounts would have to be given to exert antiseptic action in as short a time as possible, so as to get the maximum efficiency per unit of Mercurial M. The relative efficiency of these mercurials in serum or in saline for any time and concentration can be estimated by means of an equation, providing two points on the 50%

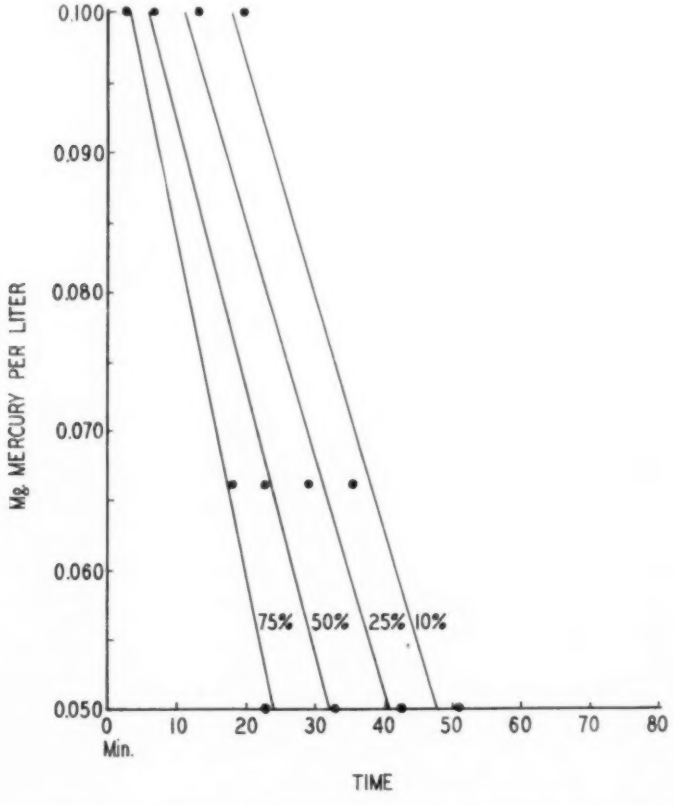

FIG. 10.—Time-concentration survival levels of a standard suspension of *E. typhosa* in mercurial M in saline.

survival level curves are known. As it has already been shown that such survival level curves are straight lines, these lines can be extended from two points to get the effect of any concentration within reasonable limits. If we let the standard efficiency of any mercurial equal 1 at that concentration on the survival level curves at which 50% of the organisms are killed in 30 minutes, then the relative efficiency of that mercurial in killing 50% of the same suspension of organisms at another concentration becomes:

$$1 \times \frac{T}{t} \times \frac{C}{c} = \text{Relative efficiency}$$

T = Standard time = 30 minutes.
t = Time required to kill 50% of the organisms at the concentration being investigated.
C = Standard concentration.
c = Concentration being investigated.
1 = Standard efficiency (unity).

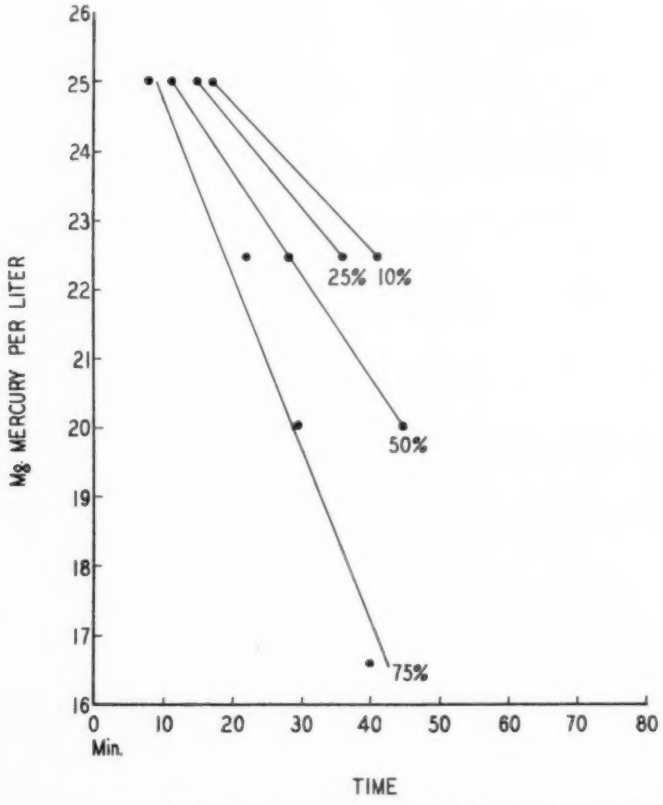

FIG. 11.—Time-concentration survival levels of a standard suspension of *E. typhosa* in mercurial M in serum.

Where the standard efficiency is unity, it must be multiplied by the standard time over the time being investigated to provide for change in efficiency due to time, and this result must be multiplied by the standard concentration over the concentration being investigated to provide for change in efficiency due to concentration. This gives the relative efficiency of the concentration being investigated as efficiency changes with time and concentration. The proportionality of the survival levels as to time and concentration are not of the first order, but of the second order, as in the following

example when the concentration of Mercurial M is slightly raised when it acts on the standard suspension of organisms in serum (Fig. 11):

$$1 \times \frac{C}{c} = \frac{22.5}{25} = .9 \qquad \frac{T}{t} = \frac{30}{15}$$

$$1 \times \frac{C}{c} \times \frac{T}{t} = .9 \times \frac{30}{15} = 1.8$$

Thus raising the concentration of Mercurial M one-ninth when it acts on bacteria in serum at the 50% survival level, increases its efficiency almost twice. The other mercurials increase in efficiency with concentration.

Similar survival level curves have been prepared for the other antiseptics studied, and their efficiency can be compared with that of Mercurial M by an inspection of Table 1. Table 1 shows the

TABLE 1.—RATIO OF COMBINATION OF MERCURIALS WITH BACTERIA AND WITH SERUM IN MILLIGRAMS OF MERCURY PER LITER.

Mercurial.	1. With bacteria, mg. Hg.	2. With serum, mg. Hg.	3. Ratio of combination.
Merthiolate	0.0062	87	14,000
Mercurochrome	0.1340	110	800
Mercurial M	0.0530	22	410
Mercuric chlorid	0.0160	7.6	300

amounts of mercurials, as mercury, necessary to kill 50% of the standard suspensions of organisms used in 30 minutes. The data in this table have been derived from the survival level curves.

The figures in Column 1, Table 1, represent the amount of mercurial as mercury necessary to kill 50% of the standard suspension of organisms in 30 minutes. Column 2 represents the amount of mercurial, as mercury, necessary to accomplish the same degree of killing in the same time, in the presence of 80% serum. As has already been shown, the figures representing the reaction of the mercurials with bacteria in serum represent the sum of two distinct reactions of the first order, represented by the equation:

$$A + B + C = AC + AB + C + B$$

where B + C equals unity, and where A represents a quantity of mercurial, and B and C represent bacteria and serum respectively. The figures in Column 1, Table 1, represent AB of the equation, whereas the amount of mercurial combined with bacteria and serum is represented by AB + AC. Therefore, the quantity of mercurial combined with the serum proteins is the quantity AC. By subtracting AB from AB + AC, or the figures in Column 1 from the figures in Column 2, we obtain the exact figure for the amount of mercurial combined with the serum proteins. This gives us a basis for determining the ratio of the amount of mercurial combined with bacteria and the amount combined with the serum proteins,

$$1 \times \frac{T}{t} \times \frac{C}{c} = \text{Relative efficiency}$$

T = Standard time = 30 minutes.
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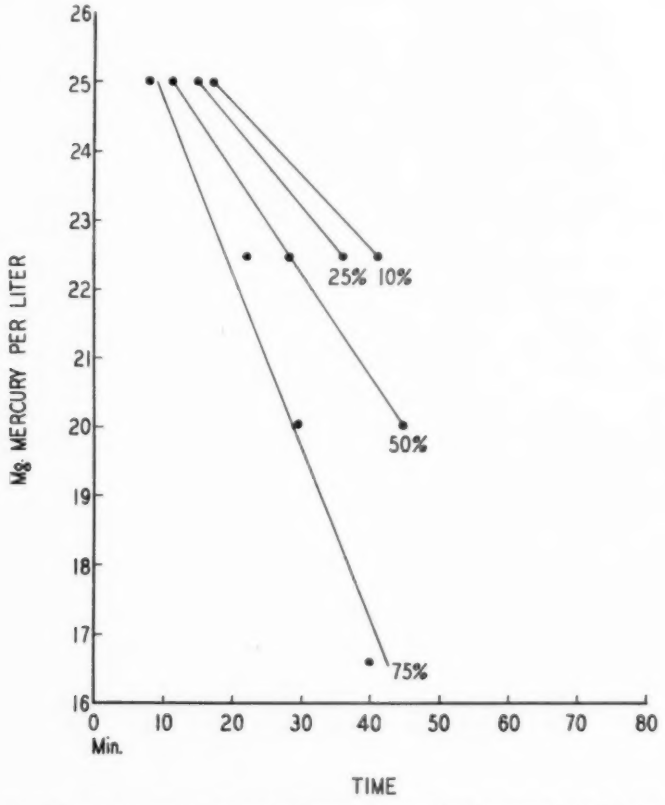

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Mercuric chlorid	0.0160	7.6	300

amounts of mercurials, as mercury, necessary to kill 50% of the standard suspensions of organisms used in 30 minutes. The data in this table have been derived from the survival level curves.

The figures in Column 1, Table 1, represent the amount of mercurial as mercury necessary to kill 50% of the standard suspension of organisms in 30 minutes. Column 2 represents the amount of mercurial, as mercury, necessary to accomplish the same degree of killing in the same time, in the presence of 80% serum. As has already been shown, the figures representing the reaction of the mercurials with bacteria in serum represent the sum of two distinct reactions of the first order, represented by the equation:

$$A + B + C = AC + AB + C + B$$

where B + C equals unity, and where A represents a quantity of mercurial, and B and C represent bacteria and serum respectively. The figures in Column 1, Table 1, represent AB of the equation, whereas the amount of mercurial combined with bacteria and serum is represented by AB + AC. Therefore, the quantity of mercurial combined with the serum proteins is the quantity AC. By subtracting AB from AB + AC, or the figures in Column 1 from the figures in Column 2, we obtain the exact figure for the amount of mercurial combined with the serum proteins. This gives us a basis for determining the ratio of the amount of mercurial combined with bacteria and the amount combined with the serum proteins,

represented by AC/AB. These ratios are given in Column 3, Table 1. It at first appears that Merthiolate is the best antiseptic studied, as only 0.0062 mg. of Merthiolate, as mercury, is required to kill 50% of the standard suspension of organisms, whereas larger amounts of the other three mercurials are required. The efficiency of Merthiolate, when used in amounts great enough to kill all of the standard suspension of organisms is very poor. When used in the presence of 80% serum, its efficiency is reduced 14,000 times as 87 mg. of this antiseptic, as mercury, combine with 1 liter of normal horse serum in 30 minutes, with a beginning concentration great enough to kill 50% of the standard suspension in 30 minutes. The ratios in Table 1 then represent the number of molecules of mercurial inactivated by the serum proteins for each single molecule used in killing the bacteria. The difference in ratio for the different mercurials can be attributed to their different reaction rates, of which the ratio is a measure. Thus, even though Merthiolate has a rapid reaction rate, and therefore appears to be a useful antiseptic in saline, this same rapid reactivity in the presence of serum makes its inactivation by the serum proteins very rapid. As the greater portion of the mercurial combines with the serum, as evidenced by the ratios (Table 1), these ratios then become a measurement of the efficiency in serum of the antiseptics studied; the ratio is an inverse function of the efficiency in serum.

3. *The Mercurials as Intravenous Antiseptics.* As the mercurials were considered for intravenous antisepsis, the total amount necessary to kill the organisms becomes of importance. It is evident from Table 1 that mercuric chlorid, from this viewpoint, is the least bad of the four antiseptics studied, as less of it is required than of the others to kill 50% of the standard suspension in serum under standard conditions, and its ratio of inactivation is among the lowest of the four mercurials studied. These ratios of inactivation must be taken into consideration, as they depend upon time and concentration, and therefore upon the efficiency of the mercurials studied.

It has also been noted that Merthiolate has a tendency to decompose with time, even in the dry state, with a subsequent loss of bactericidal activity, in saline or serum.

4. *Purified Mercury-Protein Compounds.* By a series of chemical experiments, it has been possible to determine the maximum combining power of serum with the mercurials studied. The maximum quantity of either mercurial which might combine with serum was estimated from the plating experiments. A quantity of each mercurial in excess of this amount was added to four separate 1-liter amounts of normal horse serum. The mixtures were allowed to stand 24 hours, as maximum combination takes place in this time. The excess mercurial was removed by means of electro-ultrafiltration as described by Czarnetzky.[3] By means of this procedure, all

particles of smaller dimensions than protein molecules were removed. Electro-ultrafiltration was considered to be complete when the ultrafiltrate was free of mercury and no longer bactericidal. The mercury-protein compounds were then analyzed for mercury by a modified Pregl electro-deposition method. In this method the mercury-protein compound is first digested with fuming nitric acid and Superoxyl in a wet combustion, and then placed in a glass vessel containing a weighed solid gold cathode, and a platinum anode. A current of 3.5 volts is applied for 1 hour at 50° C. The temperature is then lowered to near 0° C. The gold cathode is removed while the current is still being applied, dried, and weighed.

5. The *Maximum Combining Power of Serum Proteins with Mercury.* In Table 2 the maximum amount of mercurial, as mercury, combined with 1 liter of normal horse serum is given.

TABLE 2.—MAXIMUM AMOUNT OF MERCURIAL COMBINING WITH 1 LITER OF NORMAL HORSE SERUM IN GRAMS OF MERCURY PER LITER.

Mercurial.	Mercury combined.
Merthiolate	0.39
Mercurochrome	0.29
Mercurial M	0.35
Mercuric chlorid	0.29

Each of the mercurials combines with serum to about the same extent; approximately 0.35 gm., as mercury, per liter.

6. *Bactericidal Power of Mercury-Protein Compounds.* Strangely enough, not only are these mercury-protein compounds not bactericidal in the slightest degree, but bacteria grow readily in solutions of these compounds. This is an indication that all of the mercury present is bound by the protein. These compounds are also hydrolyzed by trypsin, as indicated by the formol titration. In these compounds only the mercury portion of the antiseptic molecule is bound to the proteins. The other portion of the antiseptic molecule is present almost entirely in the ultrafiltrate. Portions of these compounds containing approximately 0.35 gm. of mercury per liter were adjusted to pH 7.0 and then were plated with equal volumes of the standard suspension of organisms used, after allowing the mixtures to stand for 1 hour. Table 3 gives the results of such plating experiments.

TABLE 3.—BACTERICIDAL ACTION OF PURIFIED MERCURY-PROTEIN COMPOUNDS (MAXIMUM NON-POLAR COMBINATION).

Protein-mercury compound.	Dilution.	Effect.
Mercurial M	1:1	No killing
Mercurochrome	1:1	No killing
Merthiolate	1:1	No killing
Mercuric chlorid	1:1	No killing

It is obvious that protein-mercury compounds containing no unbound mercury are not bactericidal. They are not even bacterio-

static. We have observed growth of *E. typhosa* in them after 48 hours' incubation at 37° C.

7. *Mixtures of Serum and Mercurials.* On the basis of the quantities given in Table 2, amounts of each of the mercurials 10% less than the amounts combined with 1 liter of normal horse serum were added to other 1-liter lots of the same serum. These mixtures were allowed to stand 24 hours.

It was found that these mixtures exerted very little antiseptic action, as the mercury was combined with the proteins in a true non-polar stoichiometrical combination. When serial dilutions were made and plated with the standard suspension of organisms, the amount of antiseptic activity possessed by the serum-mercurial mixtures was found to be very slight, even after 1 hour of contact with the organisms. This can be seen in Table 4. As all components

TABLE 4.—BACTERICIDAL ACTION OF MIXTURES OF MERCURIALS AND SERUM ON *E. typhosa*.

Dilution of mixture.	1:1.	1:4.	1:8.	1:16.	1:20.	1:200.
Mercurial M	0	0	0	x	x	x
Mercurochrome	0	0	x	x	x	x
Merthiolate	0	0	x	x	x	x
Mercuric chloride	0	0	0	x	x	x

0 indicates no growth. x indicates growth.

of the antiseptic molecules were present in these mixtures, it can be concluded that these antiseptics exert their action on bacteria almost wholly by virtue of their mercury content.

When normal horse serum is dialyzed, the dialysate has a very slight inactivating action, demonstrable only against very dilute solutions of mercurials. This is probably due to such actively reducing substances as cysteine. Plating experiments show that traces of cysteine abolish the bactericidal action of dilute solutions of Mercurial M in saline.

Experiments are in progress designed to identify those groups in serum proteins which are responsible for the inactivation of mercurials.

Discussion. Kobert[4] gives 180 mg. of mercuric chloride as the lethal dose by oral administration. The maximum amount of mercury, in the form of any of the mercurials studied, that can combine with the blood serum of an average patient is approximately 1 gm., assuming the serum volume to be 2½ liters. This leaves out of consideration the fibrinogen, tissue proteins, intima of the bloodvessels, blood corpuscles, and so forth. The figure of 1 gm. for the total combining capacity of the proteins with which intravenous mercurials come into contact is therefore a minimum.

From the plating experiments it would take at the very least 250 mg. of Mercurial M, acting in 30 minutes, to kill one-half of the organisms in the blood stream of the average patient, with no margin of safety for the combination with other body proteins.

This figure is again beyond the lethal dose of mercury, and obviously these mercurials cannot be used successfully as intravenous antiseptics.

It is evident that any antiseptic to be suitable for intravenous therapy must combine with bacteria and serum in a ratio favorable to its combination with bacteria. The ratio of the combination of the mercurials which have been investigated is too greatly in favor of the proteins, with the result that they cannot be used successfully in the blood stream. It is suggested that this criterion will be a useful guide to the chemist in the search for suitable intravenous antiseptics.

These mercurials combine with serum proteins to the same degree, but at different rates. As all the experiments were carried out at 22° C., these rates would be approximately twice as great at body temperatures, favoring more rapid combination with the serum proteins. Nevertheless, in a relatively short time interval, it would seem that their fate in the animal body must be much the same. Mercury-protein compounds are very stable, as they are not broken down by the passage of a direct 110 v. current either in dilute or concentrated solutions. Therefore it would seem that the toxicity of these mercurials, when injected intravenously, except for a very few moments after injection, must be overwhelmingly the toxicity of their compounds with serum proteins. Thus unless used in large amounts, it is the mercury-protein compounds which come into contact with tissue cells and enzymes. This might well be taken into account in studies of their effect on tissue cultures,[5] or enzymes. Macht[6] found that mercurochrome was less toxic to oxidase of muscle than mercuric chloride, but when one converts his figures to concentration in terms of mercury, both mercurochrome and mercuric chloride have about the same effect. Kolmer and Lucké[7] found that the degree of tissue injury caused by different preparations of mercury appears to bear a direct relation to the actual amounts of pure mercury absorbed irrespective of the kind of preparation and route of administration. Birkhaug[1] also warned against the synergistic effect of the toxins of streptococci and mercurials on the kidney.

Summary. 1. The efficacy of certain mercurial antiseptics has been determined in saline and in serum, and survival level curves for the activity of Mercurial M on *E. typhosa* have been analyzed.

2. The activity of a mercurial antiseptic in serum is reduced to 0.33%—0.007% of its activity in saline.

3. The killing power per unit weight of mercury of all these mercurials falls off rapidly with dilution when used in the presence of serum.

4. Mercurial antiseptics exert their action almost wholly in virtue of their mercury content.

5. Analysis shows that 0.29 to 0.39 gm. of mercury is bound

irreversibly per liter of serum by the proteins in a mixture of serum and an excess of any of the mercurials studied. Hence the maximum non-polar combining capacity for serum of the mercurials studied is about the same.

6. The inhibiting effect of serum on mercurials is caused by the fact that the non-polar compounds of serum and mercury are not merely less bactericidal but are completely devoid of bactericidal action. Any killing may be attributed to unbound mercury present in excess.

7. It has been found that Mercurochrome, Merthiolate, Mercurial M, and Metaphen, like mercuric chlorid, are unsuitable for intravenous antisepsis, as they combine with the serum proteins so rapidly that they are almost wholly inactivated. This, of course, does not apply to disinfection of the skin—a subject outside the scope of this paper.

8. Amounts of any of the mercurials studied sufficient to sterilize the blood stream are many times the lethal dose.

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STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

IV. Observations on the Clinical and Graphic Manifestations Following the Revival of the Heart From Transient Ventricular Fibrillation.

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These studies are concerned with the cardiac mechanism following the spontaneous revival of the heart and the clinical manifestations which occurred simultaneously in 7 patients who have experienced transient seizures of ventricular fibrillation during the presence of

transient or established *A–V* dissociation. They are based on correlated observations obtained while the patients were in the electrocardiographic circuit and may be best appreciated from descriptions of several such episodes.

On one occasion, observations were made during and subsequent to a Stokes-Adams seizure with convulsive movements which lasted approximately 3½ minutes (Fig. A–1 and 2). The ventricular oscillations during syncope were almost uniform in shape and size and averaged 300 per minute (Fig. A–1A) until shortly before the revival of the heart when they decreased in amplitude and became irregular and of lower voltage, although of the same duration (Fig. A–2A). This transient period of ventricular fibrillation ended with a postundulatory pause (Fig. A–2B) which measured 0.56 second and was followed by complete standstill of the ventricles for a period of 13 seconds (Figs. A–2B to C).

The ventricular rhythm following this interval was initiated by a ventricular complex which was totally different from the others that followed it (Fig. A–2D). The second ventricular beat in this period of revival followed the first at an interval of 1½ seconds (R2, Fig. A–2E). This was in turn succeeded by a series of similar ventricular complexes which accelerated the ventricular rate progressively until it averaged 71.4 beats per minute within 2 minutes after the spontaneous revival of the heart (Fig. A–2F; Fig. B–1).

Five minutes later the ventricular rate slowed to 38.4 beats per minute and now the main ventricular deflections were at times wider and of higher voltage, but upright in form (Fig. B–2). The rate of the ventricles gradually increased again to 75 beats per minute and the deflections began to change their direction so that sometimes they were downward whereas hitherto they had been upward (Fig. B–3).

Within the next 5 to 10 minutes the ventricular rate was further increased from 75 beats per minute to 88.2 beats (Fig. B–4), and the main ventricular deflections now reverted from an upward direction to a downward one. They increased in height and measured 10 mm. Suddenly and abruptly the heart rate became accelerated to 150 beats per minute (Fig. B–5) and remained so for almost 7 minutes before it slowed to a level of 49.3 beats (Fig. B–7). Finally there was a gradual return to the original inherent ventricular rate and rhythm 4½ hours after the onset of the seizure of transient ventricular fibrillation.

In the meantime the auricles at first beat regularly during the standstill of the ventricles but for a short period they also slowed progressively for a few beats (Fig. A–2B, C). There then ensued a waxing and waning of their rate (Fig. B–1, 2) in which they kept pace with the ventricles until they suddenly began to fibrillate (Fig. 2–3A). The auricular fibrillation persisted even during the period of tachycardia so that the two irregularities existed simulta-

neously, but they were independent of each other and one rhythm did not apparently influence the other since complete auriculoventricular dissociation was present all the time.

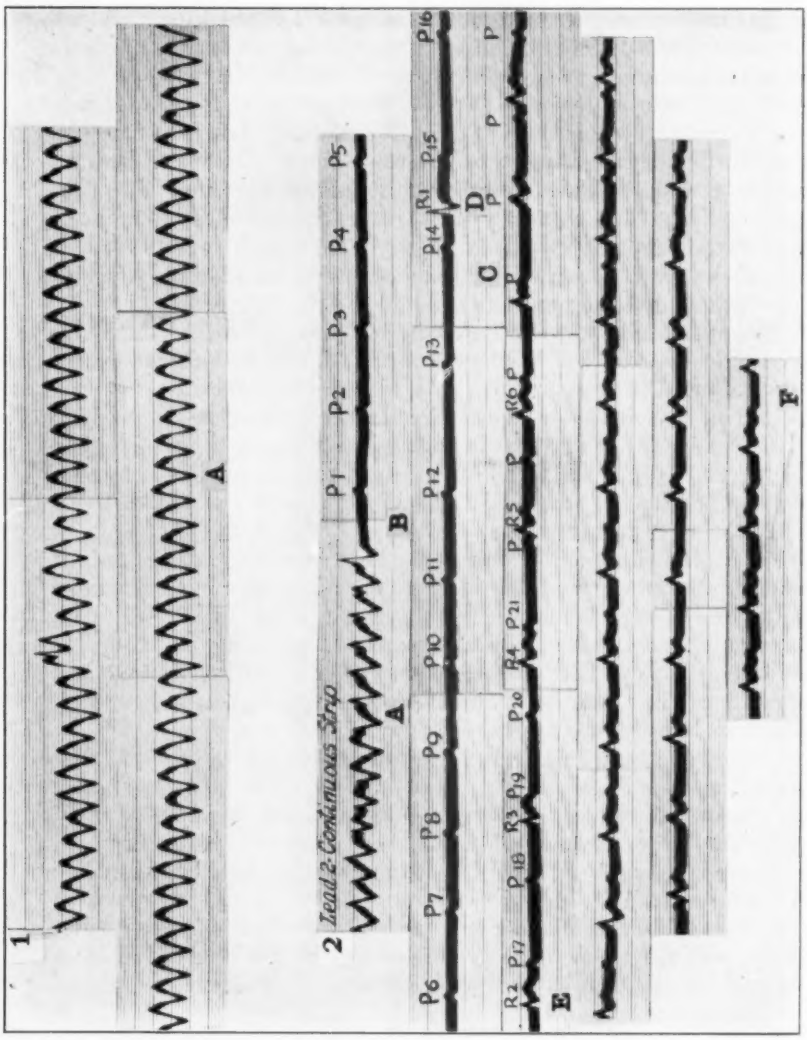

FIG. A–1.—An electrocardiogram obtained during syncope. FIG. A–2. Later records showing a period of ventricular fibrillation ended by a postundulatory pause and followed by standstill of the ventricles (B–C). This in turn is followed by a progressive increase in the ventricular rate (D–F).

During the stage of tachycardia, periodic variations in the ventricular complexes were noted (Fig. B–5A, B and 6A, B, C) which came at regular intervals, at first every tenth ventricular beat being interrupted by a variable complex, and then only every eighth beat until the heart rate returned to an average of 48.3 beats.

In this entire period the patient was in a state of stupor but could be easily aroused, although when spoken to she was very confused and did not regain full control of her senses until 5 hours had elapsed from the onset of the major syncopal attack that preceded these irregularities.

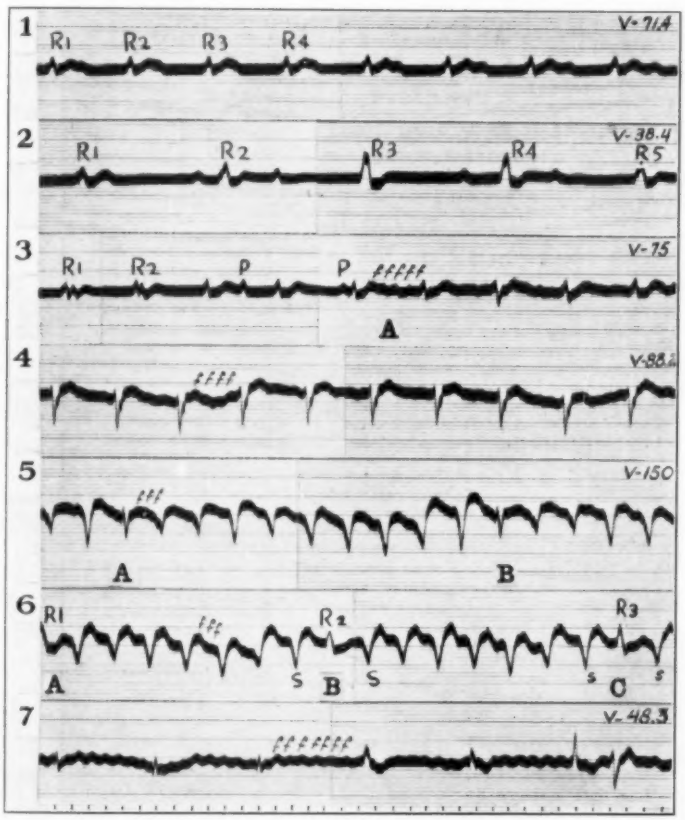

FIG. B–1.—Electrocardiograms obtained on the same patient as in Fig. A 2 minutes after the spontaneous revival of the heart. The ventricular rate now averages 71.4 beats per minute. FIG. B–2. The electrocardiogram obtained 5 minutes later. The ventricular rate has slowed to 38.4 beats per minute. FIG. B–3. Within the next 5 minutes the ventricles reached 75 beats per minute and the auricles began to fibrillate. FIG. B–4. A few minutes later the ventricular rate was 88.2 beats per minute. Note the change in direction of the main ventricular deflections. FIGS. B–5 and B–6. Now the ventricles are abruptly accelerated to 150 beats per minute and remain so for 7 minutes. FIG. B–7. The return to the basic rhythm 4½ hours after the onset of ventricular fibrillation.

The electrocardiograms of another postfibrillatory period were obtained from the same patient as the above following a seizure of transient ventricular fibrillation lasting about 4 minutes. This

long seizure of unconsciousness with epileptiform convulsions ended in apnea and the patient appeared to be dead since no heart sounds were audible and no pulsations of any peripheral vessels were visible

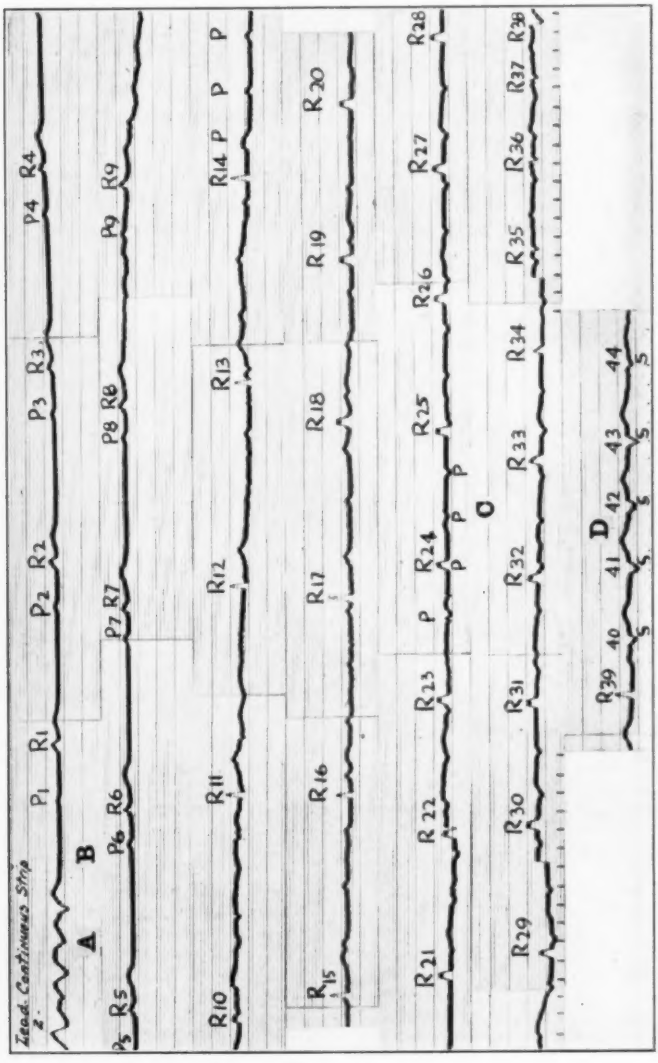

FIG. C.—An electrocardiogram showing the progressive increase in the ventricular rate following the spontaneous revival of the heart from ventricular fibrillation. Note that the auricular rate keeps pace with the ventricular rate and reaches 115 beats per minute.

or palpable. There was patchy cyanosis with lividity of the entire body as is seen in individuals postmortem. Suddenly a very faint beat could be heard at the apical region of the heart and this coincided with the appearance of a very weak pulsation at the wrist.

Exactly 2 seconds later a forceful apical beat coincided with a flushing of the face and a disappearance of the cyanosis. The patient opened her eyes 1½ minutes later, looked vaguely around

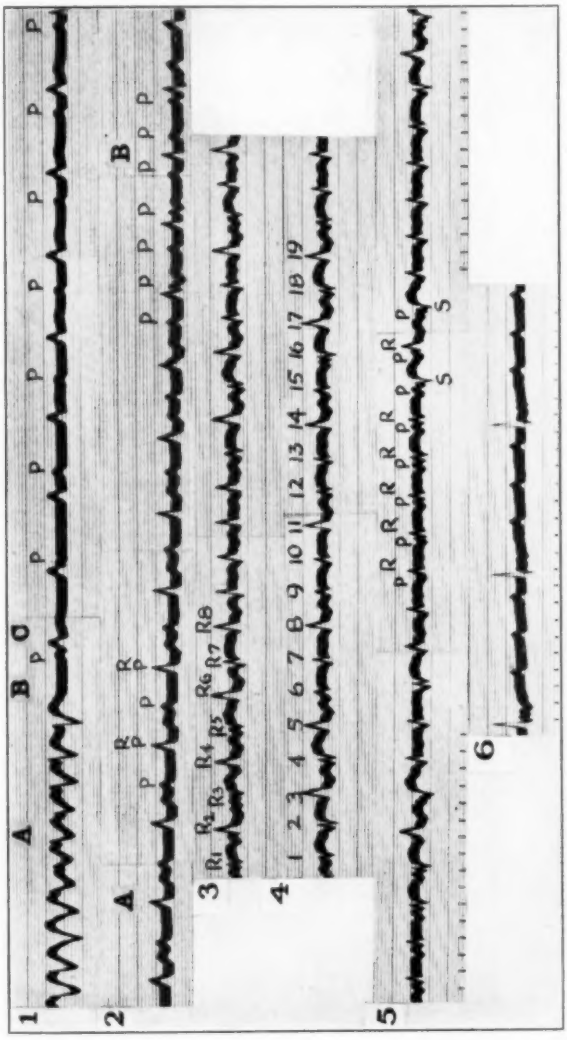

FIG. D.—The electrocardiograms obtained following the spontaneous revival of the heart from ventricular fibrillation, showing a ventricular rate of 71 beats per minute (Fig. D-1); increasing within the next 3 minutes to 77 beats per minute (Fig. D-2); suddenly accelerated to 160 beats per minute (Fig. D-3); with a final return to the basic ventricular rate of 36 beats per minute (Fig. D-6), ½ hour after revival of the heart.

in a semistuporous condition, uttered some unintelligible words and finally lifted her head at an angle and screamed very loudly, unconscious of what she was doing.

Within 2 minutes she was oriented, recognized the physicians at

the bedside and apologized for having soiled the linen since she was always incontinent of urine and of feces during her syncopal attacks.

The ventricular oscillations during this syncopal attack were wide, each measuring almost $\frac{2}{5}$ second (Fig. C–A) and spontaneous revival

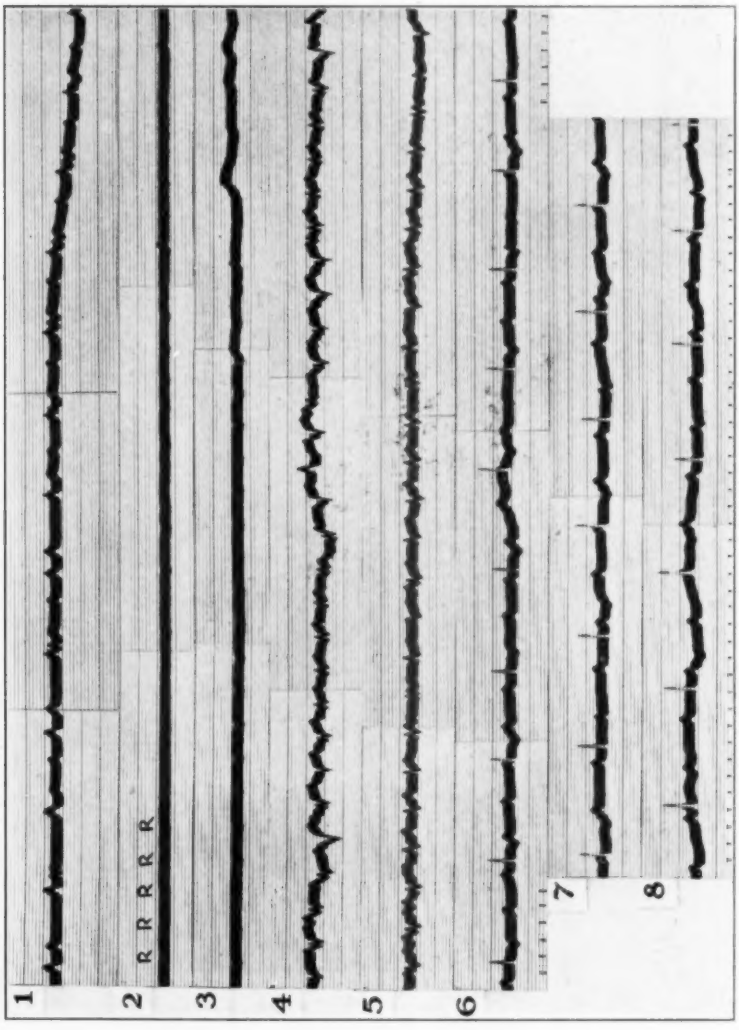

FIG. E.—The electrocardiogram showing the revival of the heart from ventricular fibrillation in a patient in whom there was a marked depression of the electrical deflections in which the ventricular complexes are barely visible (Fig. E-2 and 3). No heart sounds were audible during this period. The pulses were not palpable.

of the heart was preceded by a postundulatory pause of 1 second's duration (Fig. C–B) and was ushered in by an intermediary idioventricular rhythm with a ventricular rate averaging 24 beats per minute. An auricular complex preceded each of the first 14 ven-

tricular deflections of this intermediary idioventricular rhythm. It is questionable, however, whether there was any relationship between these auricular beats and their successive ventricular complexes, for in the early portions of this record the interventricular periods as well as the interauricular periods were constantly variable. The auricles, nevertheless, kept pace with the ventricles until the auricular rate suddenly increased to 115 beats per minute and remained so until the return of the inherent ventricular rhythm. Some of the auricular complexes became inverted after their rate had accelerated (Fig. C–D).

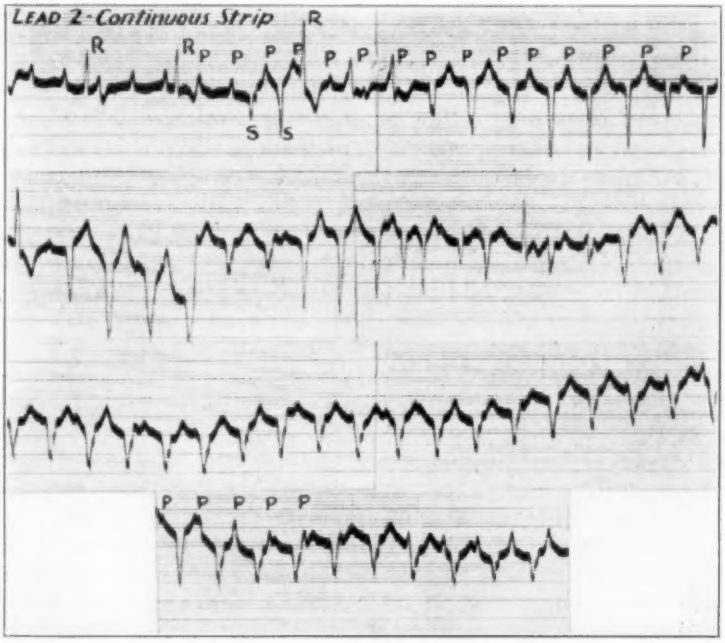

FIG. F.—Electrocardiograms showing a postfibrillatory tachysystole in which there is a sudden acceleration of the ventricles after the establishment of the basic rhythm. Such mechanisms usually heralded another seizure of ventricular fibrillation.

As the rate of the heart chambers increased progressively, the ventricular complexes also changed, reverting from a dextrogram to a levogram when they assumed a rate of 75 beats per minute (Fig. C–D).

Again, electrocardiograms were obtained from the same patient as the above at the end of a day when she was having as many as 100 syncopal attacks during a period of 12 hours. At such times when one attack appeared after another, she was completely disoriented. She moaned all the time. Her respirations were labored

and irregular. Sometimes her expirations were very short and at other times they were prolonged. She was constantly wet from incontinence of urine and she vomited all nourishment, including fluids.

An interesting phenomenon noted was that even when she had stopped having these syncopal attacks and she had regained full consciousness, the control of her urinary bladder was totally lost. Now she was incontinent all the time and this incontinence lasted for a period of 48 hours when she gradually began to regain control. Incidently, whereas hitherto she had been free from edema, now after these repeated attacks over a very short time, her face became bloated, her eyes were puffy, and all of her extremities were markedly swollen.

Similar observations on another patient were obtained after a Stokes-Adams seizure lasting a little over 3 minutes. The attack was associated with ventricular oscillations that were wide and aberrant but almost uniform in height, averaging 187 beats per minute (Fig. D–A). This seizure ended with a postundulatory pause (Fig. D–1B) and was followed by an idioventricular rhythm averaging 71 beats per minute (Fig. D–1C). Consciousness was, however, not restored during this period and with the appearance of this intermediary idioventricular rhythm, Cheyne-Stokes respirations set in and lasted for the ensuing hour.

The auricles averaged 53 beats per minute and increased in rate very gradually until within 3 minutes after the revival of the heart (Fig. D–2) they averaged 77.3 beats. The ventricular complexes during the superimposition of an auricular beat were of a different form from those that did not coincide with the *P* wave. The former were larger and more aberrant (compare Fig. D–2A and 2B).

Suddenly and very abruptly, the ventricular rate accelerated to 166 beats per minute, the auricles in the meantime keeping pace with them. Of interest in these records (Fig. D–3, 4, 5) are the variable ventricular complexes that at times alternate at every second beat and sometimes at every fourth beat. Frequently the intervals between periods of alternation were greater (Fig. D–5). The auricular complexes are clearly distinguished when this tachysystole is lowered to 150 beats per minute (Fig. D–5). When the inherent idioventricular rhythm returned to a rate of 36 beats per minute, then the auricles remained at their former rate of 136 beats for some time before they slowed to their usual average of 100 beats.

This entire postfibrillatory period lasted almost ½ hour. Similar electrocardiograms were obtained repeatedly in 5 other patients with either transient or established auriculoventricular dissociation.

In the same patient another type of cardiac mechanism was encountered at a time when the major syncopal seizure of the day was followed at first by an intermediary idioventricular rhythm

with a regular rate averaging 71 beats per minute, $2\frac{1}{2}$ minutes after the spontaneous revival of the heart (Fig. E–1).

Despite the revival of the heart, however, the patient screamed after the first few effectual beats of the heart appeared and then lapsed into coma. A period of quiescence ensued with a very marked depression in the voltage of all the complexes (Fig. E–2, 3) which could barely be distinguished, although on careful examination there is a regular periodicity in the small wavelets that are visible, their rate being 166 beats per minute.

This type of mechanism continued for only 68 seconds before it was replaced by a deflection with increased voltage resembling other records encountered previously. Compare Fig. E–4 and 5 with Fig. D–3 and 4. During these abnormal increases in the ventricular rate, the auricles beat independently of the ventricles, although the auricular rate kept pace with the ventricles.

Within 28 minutes after its onset, the postfibrillatory period slowed to a ventricular rate of 60 beats per minute (Fig. E–6) and finally 12 minutes later it resumed its level previous to that of the onset of syncope, which was 46.8 beats per minute (Fig. E–8) and remained so for the rest of the day. Cheyne-Stokes respirations which set in soon after the onset of this cardiac mechanism disappeared within 1 hour.

On several occasions it was noted that when the inherent rhythm was reëstablished very soon (within 15 to 45 seconds) after a syncopal seizure, due to ventricular fibrillation, there elapsed a few minutes, during which time the ventricles beat, slowly at first, but regularly, at a rate averaging 60 beats per minute (Fig. F–A), while the auricles averaged 187 beats. Suddenly and abruptly (Fig. F–B) the ventricles would start beating at 150 per minute and the auricles would slow to the same rate and keep pace with the ventricles for a time before either one of two conditions resulted. Sometimes the tachysystole would slow abruptly or gradually to the originally established rhythm of the ventricles during auriculoventricular dissociation or else the tachysystole would be part of the premonitory period of another seizure of transient ventricular fibrillation.

These postfibrillatory tachycardias of the ventricles were unusual in that the auricular complexes could readily be made out during the presence of aberrant ventricular complexes even though there was a waxing and waning of the ventricular rate at such times. There was a very marked variability in the size, shape, and form of the ventricular deflections comprising this increased postfibrillatory period and there is every likelihood that most of the beats originated below the bifurcations of the auriculoventricular node either in one bundle or the other.

Discussion. These observations indicate that the successive events following the spontaneous recovery of the heart after transient ventricular fibrillation are of a very distinct nature. If the

periods of ventricular fibrillation were of short duration (not greater than 50 seconds) then revival of the heart was immediately associated with the previously established inherent rhythm of the ventricles. If fibrillation was of longer duration, however, or if repeated shorter attacks preceded one single long seizure, then the successive events leading to recovery of the heart from fibrillation were more variable.

Sometime a postundulatory pause ended the transient period of ventricular fibrillation and was followed by standstill of the ventricles. This occurred both when the inherent rhythm of the ventricles alternated with the normal sinus rhythm so as to produce interference with dissociation or when there was established auriculoventricular dissociation. The postfibrillatory standstill of the ventricles varied in duration but the average of all the recorded standstill periods was $23\frac{1}{2}$ seconds. Again, instead of complete standstill of the ventricles (Fig. A–2) there occurred an irregular slowing of the ventricles in which the longest ventricular cycle appeared sometime after the recovery of the heart (Fig. C). Occasionally a period of slowing of the inherent rate of the ventricles appeared several minutes after the postfibrillatory standstill but was preceded by a moderate increase in the rate prior to this (compare the ventricular rate in Fig. A–2B to F with Fig. B–1 and 2).

It is of some interest to speculate on the reasons for the variable change in the heart rhythm observed in the immediate revival of the heart following ventricular fibrillation. It is well known since Gaskell's[1] experiments on the cold-blooded heart that the rapidity with which an idioventricular rhythm develops depends in part upon the rate at which the ventricles beat previously. In studying the behavior of the ventricles when they were dissociated from the auricles in complete heart block, Erlanger and Hirschfelder[2] observed that when an idioventricular rhythm of the isolated ventricles was increased by the application of electrical shocks, cessation of stimulation was followed by a period of slow contraction of the ventricle. The duration of the "stoppage of the ventricles" was found to depend largely upon the rate and duration of the preceding period of artificial stimulation and upon a certain "depressed" condition of the heart at the time of stimulation. These observations were subsequently confirmed by Cushny[3] and attributed by him, in addition to the rate and duration of stimulation, to a reduction of oxygen in the perfusing fluid resulting in *asphyxia*, as well as to a diminution of the perfusing fluid at such times.

Both Erlanger and Hirschfelder, and Cushny noted that there were two types of stoppages of the ventricles following artificial stimulation. In the first type, the first ventricular cycle after cessation of stimulation appeared to be the longest and in the other type the successive ventricular cycles increased in length from beat to beat for several beats before there appeared gradual acceleration

of the ventricles to their return to the inherent rhythm. In none of their experiments was the ventricular rate after the period of standstill of the ventricles found to be greater than the inherent basic rate after the establishment of auriculoventricular dissociation.

They further observed that the slowing and the pauses after cessation of artificial stimulation were generally more marked and more persistent in the latter phases than in the beginning of the experiments. As the "energy" of the heart decreased, the results of the accelerated rhythm became greater and a longer interval had to be allowed to obtain the return of the rhythm prevailing before the interference. Spontaneous acceleration of the ventricles were similarly observed to result in periods of slow ventricular rhythm. Cushny concluded that this low phase was not inhibitory in the origin since it occurred after full atropinization of the animal as well as before. He felt the phenomenon was due to a depression of the function of stimulus formation in the ventricular pacemaker which presents analogy to the fatigue of striated muscle and that the contractility and excitability of the ventricles was not diminished at such times.

It would appear that the cardiac mechanisms observed in the postfibrillatory period in man are an almost exact parallel to the experimental studies cited above. It is conceivable that the repeated spontaneous accelerations of the heart which take place in human beings prior to and during transient ventricular fibrillation, progressively augment the fatigue of the ventricular pacemaker so as to depress its function and thus result in stoppage of the ventricles.

Since standstill of the ventricles after transient ventricular fibrillation is a natural phenomenon and is directly related to the immediate previous alteration in the rhythm of the heart, it is a fallacy to assume that the administration of any drug during a period of such postfibrillatory standstill is responsible for the revival of the heart. This was suspected by Levine and Matton[4] in 1 of their patients with transient ventricular fibrillation in whom standstill of the ventricles was followed by revival of the heart after the intracardiac administration of adrenalin. As a matter of fact, as we have pointed out elsewhere, adrenalin in any form is contraindicated in patients who are subject to transient seizures of ventricular fibrillation for in such patients the drug precipitates and may perpetuate the fibrillary process.[5]

The Behavior of the Auricles in the Postfibrillatory Period. It has been pointed out that the auricular rate and rhythm are, as a rule, undisturbed during short runs of ventricular fibrillation, although at times it is difficult to distinguish the superimposed auricular waves upon the ventricular deflections during ventricular fibrillation. During longer runs of ventricular fibrillation, the bizarre ventricular complexes obscure completely the auricular waves and we can

only assume from experimental observations that the auricles at such times may be reflexly stimulated above their basic rate by retrograde impulses from the fibrillating ventricles. Consequently, since the auricles are dissociated from the ventricles, this effect of extra stimulation upon them results in their slowing after the cessation of fibrillation of the ventricles. We then have the same variability in the rate and rhythm of the auricles in the postfibrillatory period as was described for the ventricles. These consist of variable pauses with a waxing and waning of the rate until the inherent rhythm is established again. On rare occasions the auricles may even begin to fibrillate or flutter for a short period and continue fibrillating even though the inherent rate of the ventricles has already been reëstablished. Mention should be made that since the longer runs of ventricular fibrillation are invariably associated with high grades of apnea, part of this auricular and ventricular slowing may be attributed to asphyxia, an experimental phenomenon well known to produce various grades of block.[6]

The Postfibrillatory Tachycardias. The slowing of both auricular and ventricular rates after the cessation of ventricular fibrillation is usually followed at a variable interval by a progressive increase in their rates until the reëstablishment of their inherent rhythms. But, as has been pointed out above, there frequently ensues after the reappearance of this inherent rate a second period of acceleration of both the auricles and the ventricles. At times, this is a gradual affair (Fig. B–3, 4, 5, 6) in which the ventricular rate is augmented by a shortening of the interventricular periods until a maximum rate of 150 to 160 beats per minute is reached. The ventricular deflections during these tachycardias are aberrant and totally different from those of the basically inherent rhythm. It is very likely that an ectopic focus within the ventricles or in one of the bundles assumes the pacemaker at such times and after persisting for a while gradually gives way to the inherent rhythm of the ventricles.

Occasionally an ectopic focus within the ventricles may suddenly disrupt the basic rhythm (Fig. F) and initiate a tachycardia with variable ventricular complexes and an irregular ventricular rate, during which the auricles keep pace with the ventricles. The return to the inherent rhythm of both the auricles and ventricles in these instances has been observed to be gradual.

More often, this second period of acceleration of the ventricles may be associated with a bidirectional type of tachycardia (Fig. D–3) with ventricular complexes that alternate periodically at various intervals (Fig. D–4).

It was following the repeated presence of such tachycardias of the heart over several days at a time, after innumerable recurrent seizures of transient ventricular fibrillation, that these patients

invariably developed signs of severe congestive heart failure, whereas throughout their entire period of freedom from Stokes-Adams seizures, they never showed any such signs.

Summary and Conclusions. 1. Correlated observations were made of the clinical and graphic manifestations following the spontaneous revival of the heart from transient ventricular fibrillation in 7 patients with either transient or established *A–V* dissociation.

2. It was determined that revival of the heart from transient ventricular fibrillation in man is associated usually with a post-fibrillatory pause, followed by a variable standstill of the ventricles and an intermediary idioventricular rhythm with a progressive increase in the heart rate to as high as 160 beats per minute before the restoration of the basic ventricular rhythm.

3. The duration of this postfibrillatory period is dependent upon the duration of the antecedent period of ventricular fibrillation and is independent of the type of ventricular oscillations present during the fibrillatory period. It may vary from a few seconds to as long as ½ hour at one time.

4. The spontaneous revival of the heart from transient ventricular fibrillation is associated clinically with a sudden flushing of the face and entire skin by a pink-red coloration, a forceful pulsation of the heart against the chest wall and with a barely perceptible beat of the pulse at the wrist. With these events the eyes open and loud screaming may be followed by incoherent and unintelligible speech, a very cloudy sensorium and a progressive increase in the heart rate as noted from the electrocardiograms. This in turn is followed by a progressive lowering of the heart rate again to the original basic level prior to that present before the onset of ventricular fibrillation. Coma and a period of unconsciousness may then supervene and last as long as 5 hours after a major syncopal attack.

5. The period of apnea present during ventricular fibrillation is replaced at first by irregular periods of respirations in which inspiration is prolonged. There may then appear typical Cheyne-Stokes respirations as well as all forms of irregular respiratory movements noted after asphyxia.

6. Occasionally after repeated attacks there is a generalized anasarca, involving the face, arms and the entire skin.

7. All of these symptoms and signs are so unique that a clinical diagnosis of transient ventricular fibrillation may be suspected in an individual with syncopal seizures if they are noted after the attack.

8. Since the natural course of the revival of the heart from transient ventricular fibrillation includes a period of acceleration of the heart following a postfibrillatory standstill of the ventricles, it is a fallacy to assume that any drug administered during the post-fibrillatory period is responsible for the successive events which appear after its use.

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RADIAL ARTERY CHANGES IN COMPARISON WITH THOSE OF THE CORONARY AND OTHER ARTERIES.

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The purpose of this paper is to report observations on changes in the radial artery both at various age periods and as a result of sclerosis, in comparison with similar changes in the coronary and other muscular arteries from the same case. In doing this, we have taken the well-described coronary changes as a standard for comparison.

The radial artery has been especially investigated by Hallenberger,[1] Thayer and Fabyan,[2] Hesse[3] and others. The reasons for this are pretty obvious. The taking of the pulse rate and pressure at the radial is presumably accompanied by palpation of the vessel wall in an endeavor to estimate the absence, presence and degree of arteriosclerotic change with possible inference from this as to sclerotic changes elsewhere. It is as an index of general or visceral arteriosclerosis that the radial artery has received particular attention. Hallenberger, noting the paucity of accurate investigations of arteries possibly involved in arteriosclerosis such as the radial, undertook such a study at Aschoff's request. He examined histologically the radial artery in about 80 cadavers, ranging in age from 8 months to 75 years and attempted to discriminate between physiologic and pathologic alterations in the vessel. Thayer and Fabyan's work is a clinico-pathologic study of the radials in 61 cases, comparing palpability and thickening with histologic findings and concluding that the unduly palpable radial artery is a danger signal of very possible visceral sclerosis. Hesse's

exhaustive monograph includes the removal in one piece of the subclavian, axillary, brachial and radial arteries and a gross and microscopic study of all these vessels, which permitted contrastive observations on normal and arteriosclerotic changes in vessels of both the elastic and muscular types of the upper extremities. In this way, she examined 41 cases at ages ranging from 2 days to 79 years and in addition a 6½ months' fetus. Though the amount of her material was small, she concluded that palpability of the arteries was independent of any morphologic change and due to tension and tonus of the vessel wall. Fischer and Schlayer[4] many years previously had advanced a similar opinion based on a comparative test of the palpability and of the anatomic findings carried out on 75 arteries. They examined in each case the radial, brachial, femoral and carotid. In 50% of the cases where an intimal sclerosis was present, no thickening of the arterial wall could be demonstrated. In 75% of the cases where a very marked thickening or palpability of the artery was found, there was no anatomic sclerosis of the intima. The majority opinion seems to favor the view that the clinical condition of the radial artery offers no accurate information as to arterial conditions elsewhere. We, therefore, did not approach the problem from this angle.

In a series of 86 cases, ranging in age from birth to 84 years, we examined in each instance the radial and coronary arteries, in 25 cases the renal and splenic arteries as well, and in 7 cases a cerebral vessel also. We further studied 35 additional coronaries without accompanying radials. In each of the 86 cases, sections were taken from the anterior descending branch of the left coronary, the left circumflex and the right coronary arteries and the radial artery at the wrist. These were stained with hematoxylin and eosin and with Weigert's elastic stain and van Gieson. The same procedure was followed when other arteries were sectioned. While there was a certain amount of gross inspection in selecting the most likely part for section, the study was essentially microscopic and involved the examination of about 1700 sections.

The age distribution of the 86 cases as to decades was as follows: First, 6; second, 9; third, 9; fourth, 6; fifth, 23; sixth, 10; seventh, 17; and eighth and above, 6. The additional 35 coronary cases were likewise distributed through various decades. There was a partial selection of cases utilized in that we endeavored to get an average of individuals and ages that would represent what might be termed the normal age evolution of the vessels especially in the later years; and, again, another selection of cases suffering from diseases promising a maximum result in the way of vascular change. There were 73 males and 48 females in the series but we did not attempt an analysis on a sex basis.

Our scheme of procedure was first the systemic examination of the 121 available coronary arteries distributed widely through the

various decades. Thanks to the definite, clean-cut and extraordinary changes which take place normally and pathologically in these vessels and the detailed expositions of them by Wolkoff,[5] Ehrich, de la Chapelle and Cohn,[6] and Gross and his colleagues,[7] the order and degree of their physiologic and pathologic change is almost standardized and to a lesser extent for muscular arteries generally.

The large coronary arteries show, both as to incidence and degree, among the greatest changes of any arteries in the body; this is especially the case with reference to muscular arteries, of which the coronary is an example. And among the elastic arteries, the aorta only approaches them in extent and frequency of alteration. Beginning with birth, plainly demonstrable changes are seen in even the first few weeks and continue until death, so that at 60 or 70 these vessels present a histologic picture that only remotely resemble the artery of the first decade. For details of this lifelong evolution, one should consult Gross' article. Both physiologic and pathologic changes are predominantly intimal. At birth or in the first week, there may be slight thickening and beginning splitting of the internal elastic layer of the intima. This increases and longitudinal smooth muscle fibers appear between the split elastica. This constitutes the musculoelastic layer. The innermost elastic layer, the "secondary intimal elastic membrane," splits further to form the elastic-hyperplastic layer. The inner portions of the elastic-hyperplastic layer develop a preponderance of connective tissue and form the connective tissue layers. All of these layers, the musculoelastic, the elastic-hyperplastic and the innermost connective tissue layer progressively increase in thickness, mingle more or less, and collectively form an outstanding thick intimal layer soon equal to and often much thicker than the media. While these changes are taking place, straightening out of the usual undulations and breaks are seen in the internal elastic layer, and longitudinal muscle fibers from the media push over the intimal border causing "border disappearance" and constituting an "intermediary layer." Usually, however, it is quite easy to distinguish between the intimal and medial coats. The fine elastic fibers of the media first increase with years and then decrease and collagen fibers ultimately appear. But the media as well as the adventitia offer insignificant changes compared with the intima. All these coronary changes develop to reach a maximum about the end of the fourth or fifth decade and thus far the mural evolution is usually regarded as physiologic. Whether physiologic or pathologic, such intimal alterations are rather characteristic of muscular arteries as a whole. In other words, thus far, the coronary arteries act, as they look, like muscular arteries. After the fourth decade and especially in the sixth, atherosclerosis appears and caps the previous marked thickening with an eccentric addition which tends

considerably to narrow the lumen of the vessel. The media now suffers pressure atrophy and thins considerably. Both Wolkoff and Beneke[8] emphasize the localization of these eccentric thickenings on the side of the artery that is turned toward the heart, the part that rests against the heart muscle. Another favored site is at the origin of branches. In fact, arterial thickening of any type seems to be especially prone to appear where branches leave the larger vessel. Following atherosclerosis, necrosis and calcification are common. It will be noted that this calcification, like the atherosclerosis, is intimal and scarcely ever is it found in the media. Here, therefore, the coronary acts like an elastic artery in which calcification, if it occurs, is regularly intimal. Ophüls[9] thinks that from Wolkoff's description of the large branches of the coronaries, they resemble partly the elastic and partly the muscular arteries. The atherosclerotic changes are usually regarded as pathologic, with Wolkoff dissenting. Whatever the viewpoint, it is evident that such extreme alteration and thickening of the wall may lead to practical lumen extinction, either directly or finally through thrombosis.

Our sections of coronary vessels showed these changes quite clearly. Coronary vessels from 2 stillborns showed a perfect single-layered internal elastic layer. At 3 and 7 days, there was a little thickening. An artery of a 10-day-old infant exhibited definite elastic splitting and at 5 weeks a case showed a distinct musculo-elastic layer. At 2 months, the anterior descending branch of 1 case showed almost no change, while the right coronary showed splitting and an elastic muscular layer. At 1 and 3 years, these alterations were pronounced but still relatively slight. As the age increases, the intimal layer progressively and for the most part steadily thickens with one or more of the three layers described more or less prominent. Thus up to 40 or 50 years of age what one sees with not too analytic an eye is a gradual thickening of the intima as a whole. This gradually growing intimal collar seemed to us to be fairly uniform for the entire circumference of the vessel, though occasional thickenings were seen, notably at the branching of a vessel. There certainly was not the marked eccentric disposition seen in atherosclerotic formations. The degree of intimal thickening may be rather satisfactorily gauged by noting roughly its relation to the thickness of the media. Thus, the ratio of intima to media in thickness at birth and shortly after may be 1 to 6 or 8, after the first year and up to the tenth the ratio may be 1 to 2 or 3 and occasionally 1 to 1. In the second decade the ratios of intima to media do not vary much from the last of the first decade. But in the third decade, they are commonly 1 to 1 and not infrequently 2 to 1 or 3 to 1. The same ratios hold for the fourth decade. But again in the fifth decade, especially the latter half, the intima is found to be 2 to 3 times the thickness of the media and occasionally

higher with ratios 4 or 7 to 1 (atherosclerosis). In the sixth decade, ratios of 5 or 10 to 1 are common, due to the frequent appearance of atherosclerotic thickenings. Where atherosclerosis is absent, the ratio does not vary much from that seen in the fourth decade. The alternation of ratio is dependent almost entirely upon intimal change rather than medial. The coronary arteries, then, from birth to death gradually thicken, almost exclusively through intimal change. Up to 40 years this is roughly uniform and may be considered hyperplastic and physiologic. After 40 there is not much change of this type, but commonly supplementary eccentric addition to the intimal thickness by atherosclerotic formation. This may be totally expressed in the altering ratio of intimal to medial thickness and this may be considered an index of coronary sclerosis, physiologic or pathologic.

Radial artery changes have been analyzed generally along the same lines, Hallenberger, Thayer and Fabyan and particularly Hesse describe primary splitting of the elastica with the development of the elastic muscular layer, then the elastic-hyperplastic layer and finally the connective tissue zone or thickening. Upon this may or may not be superposed atherosclerosis: all agree that in the radial this is uncommon if not actually rare. The radial is a much smaller artery than the main coronaries and the changes in it are infinitely less than in the coronary and proportionately difficult to analyze meticulously.

Surveying our sections of 86 radials in advancing decades, we observed in the radial of the stillborn the perfect single-layered internal elastic layer immediately beneath the lining endothelium as in the coronary. At 1 and 3 years of age, splitting of the internal elastic layer was seen, but little else except a very slight thickening where branches leave. Toward the end of the first decade, there may be noted a very slight thickening in addition to splitting, the beginning of the musculoelastic layer. Radials at 12, 13, 14, 16 and 17 years showed only a slight exaggeration of this, changes that ordinarily would be passed over. One radial at 16 years exhibited almost no alteration. In radials at 12, 13 and 14 years, the media appeared thickened but we thought this might be due to the postmortem contraction of the arterial wall that Hesse found so marked in the young. From 21 to 30 years, this thickening of the intima, due to splitting and proliferation of the elastic layer, together with the appearance of muscular and connective tissue fibers, progressed steadily but only to a very slight degree. Again in the fourth decade, from 31 to 40, the increase continued but not greatly. In this decade one could see in the Weigert sections definite multiple elastic layers and in the hematoxylin and eosin sections an increased breadth of intima dotted with cross-sections of nuclei and fibers. There was a decided increase of thickening in the fifth decade, from 40 to 50 years, in which we were able to

examine 17 radicals. There now was seen a distinct though slight intimal collar made up mostly of split elastica and connective tissue. Longitudinal sections showed connective tissue arranged lengthways between the elastic layers. There is supposed to be a certain amount of longitudinally arranged unstriped muscle with this connective tissue, but it is difficult to distinguish even with the van Gieson stain. From 50 to 60 and from 60 to 70 there was still a fairly steady though not excessive increase in the thickness of the intimal wall. Most of the radical change is intimal and this intimal change occurs particularly between 45 and 65. After 65 there is not much intimal thickening, but as the media shows some degeneration and slight thinning particularly after 60, casual observation may give the impression of rather marked intima increase. We measured the medial of all radials and found the thickness of the middle coat increased up to the middle of the third decade, after which it remained practically stationary until the middle of the seventh decade, when the media showed a slight thinning. All this change is of the type seen in the coronary and usually regarded as physiologic, though in the radial the discrimination between musculoelastic, elastic-hyperplastic and connective tissue layers is much more difficult, if not at times impossible, on account of the greatly less degree of alteration. Atherosclerosis as it occurs in the coronary is, for practical purposes, not seen in the radial. On this paucity of lipoid deposit or atherosclerotic formation all writers agree, and Nordmeyer[10] found no fat in the radial artery. Her sections, like ours, were taken at the wrist. She refers to the fact that Hesse in higher sections of the radial found more sclerosis. In our series of 86 radials, we found only in 3 evidences of slight lipoid deposits in the thickened intima and in no case any atherosclerotic plaques. Certainly the striking extreme eccentric atheromatous thickening so characteristic of the coronary is not seen in the radial. The maximum change in the radial artery, consisting of a roughly uniform intimal collar of elastic and fibrous connective tissue and achieved between 45 and 65 years is comparable in kind but not in degree with the probably physiologic variety seen in the coronary before 40 years. We should say that the thickest radial seen at, say 65 years, and above, compared in kind and degree with that of the coronary change at about 20 years of age.

These differences in radial and coronary vessels are strikingly brought out in a comparison of the ratios between the intima and media in the two vessels, as the changes in both arteries are dominately intimal. In comparison with the intimal-medial ratio in the coronaries, previously described, in the radial, the intimal-media ratio of 1 to 8 or more found in the first decade shifts much more slowly, until between 30 and 40 years of age it may be 1 to 4 or 5. After the fourth decade, the intima thickens more and

the ratio is then 1 to 3 or 4 and later 1 to 2 or 3. Only occasionally is the ratio 1 to 1, the intima equalling the media in thickness, and it exceeds the media only rarely and locally in one of the cushion-like thickenings. The difference in ratio is not due to thickening of the media, which changes but little in diameter in the radial after 30. This notable difference between radial and coronaries we have attempted to make clear in a series of comparative drawings of the radial and coronary walls drawn to scale as far as the intimal and medial ratios are concerned (Figs. 1, 2, 3 and 4). The compared radial and coronary arteries at any given age are always from the same case. The coronary is, of course, much larger than the radial and this is not seen in the drawings but the actual breadth relation between the intima and media of each vessel has been strictly maintained. The variation in intimal thickness at different ages and in the single sections is outlined in the black silhouette while the media is shown in white. They represent the progressive mural thickenings from birth to old age. We did not attempt to select or avoid cases with diseases supposedly predisposing to arteriosclerotic change, as both arteries are presumably liable. But the majority died with disease having no known definite relation to arterial change, and we think these drawings represent what may be expected in the way of change at different ages in the respective vessels. It is interesting that the coronary in the patient, aged 32, dying of acute leukemia, showed almost as much change as the coronary of the 84-year-old patient dying of nephrosclerosis and that while the radial is relatively thickened in both these cases, they were scarcely so in other cases with marked coronary thickening. It is plain from these drawings the coronaries increase early, progressively and greatly, while the radials show a relatively slight and insignificant change.

We have so far purposely omitted mention of medial calcification (Mönckeberg's sclerosis), as it apparently has no bearing on or relation to the intimal changes just discussed. Mönckeberg's sclerosis, as is well known, is a disease of muscular arteries, particularly of the peripheral vessels and is much more common in the lower extremities. Lange,[11] in 300 cases, found medial calcification in the lower femoral in 97%; posterior tibial, 87%; anterior tibial, 83%; brachial, 2%, radial, 18%; and ulnar artery, 14%. It is a pretty good rule that atherosclerosis increases centripetally and medial calcification centrifugally. Atherosclerosis attacks the elastic arteries; medial calcification, the muscular arteries. In 9 of our 86 radials there was well-marked medial calcification. This was distinctly medial and in none of our cases was there intimal calcification. Some writers, Thayer and Fabyan, for example, think intimal calcification of the radial not uncommon, but this is not our experience. Both Hallenberger and Hesse found calcification along the internal elastic layer. Some of our sections showed this appearance, but it

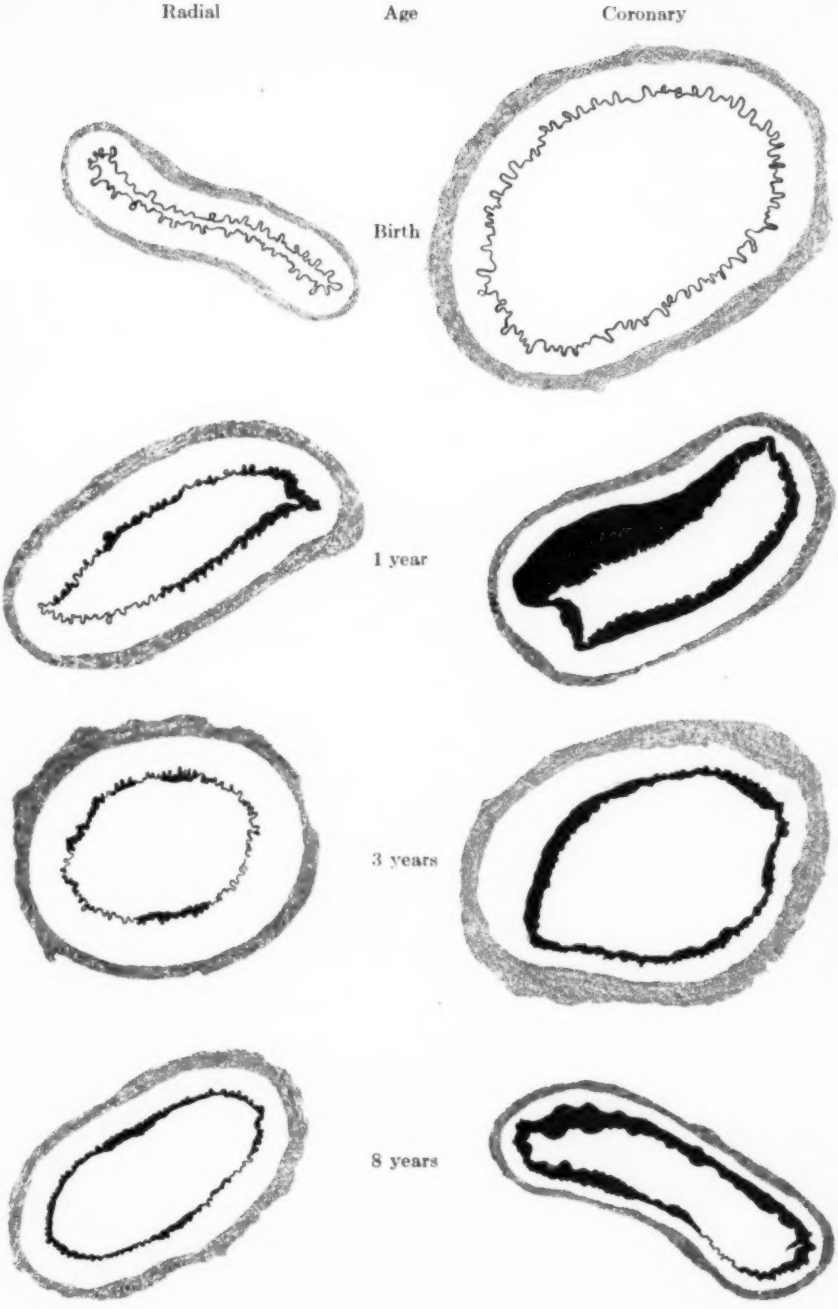

FIG. 1

FIGS. 1, 2, 3 and 4.—(34 small drawings.)* Cross-sections of the radial and coronary arteries, each from the same case, at various age periods as follows: birth, 1, 3, 8, 14, 17, 21, 28, 32, 37, 42, 49, 53, 60, 64, 70, 84 years. Intima in black, media in white, adventitia stippled, drawn to scale to show relation of intima to media in thickness.

* The accurate drawings were done by F. T. Kepler.

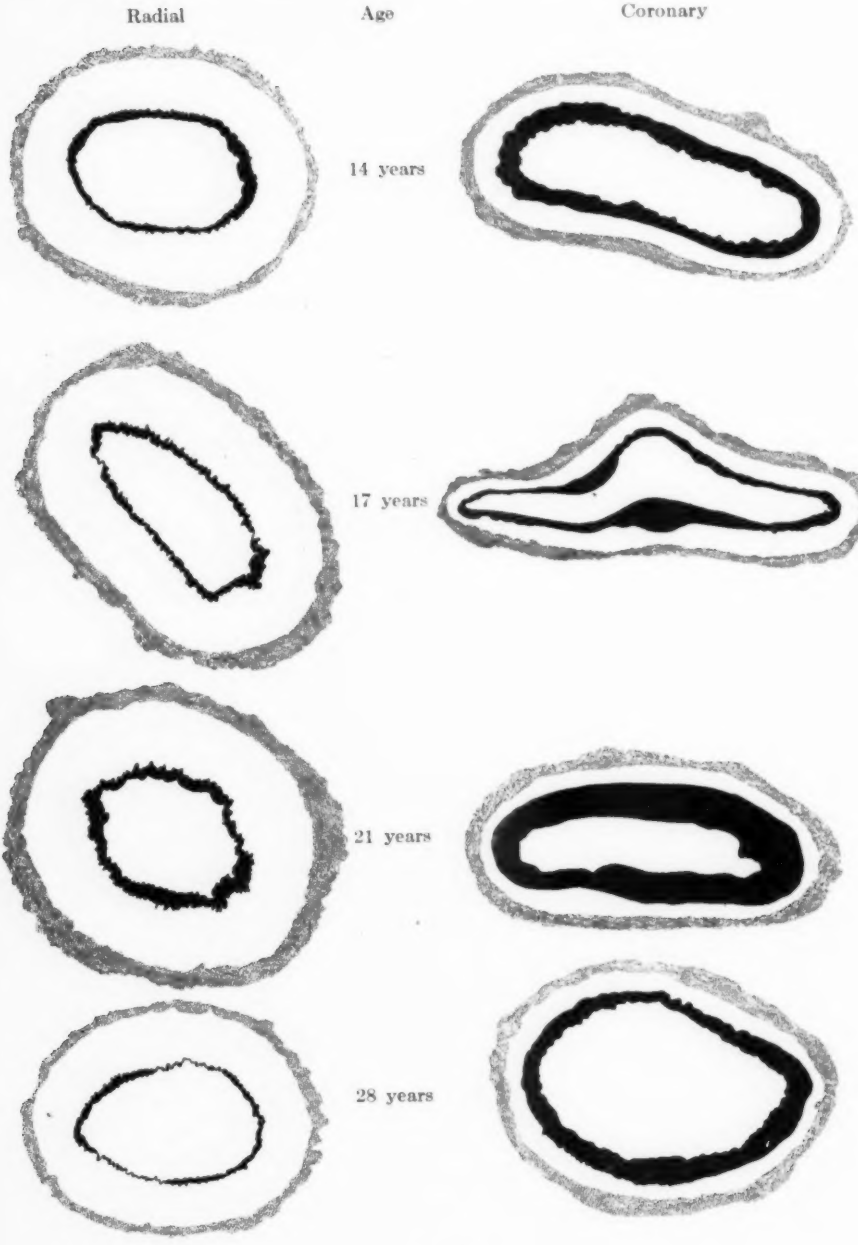

FIG. 2

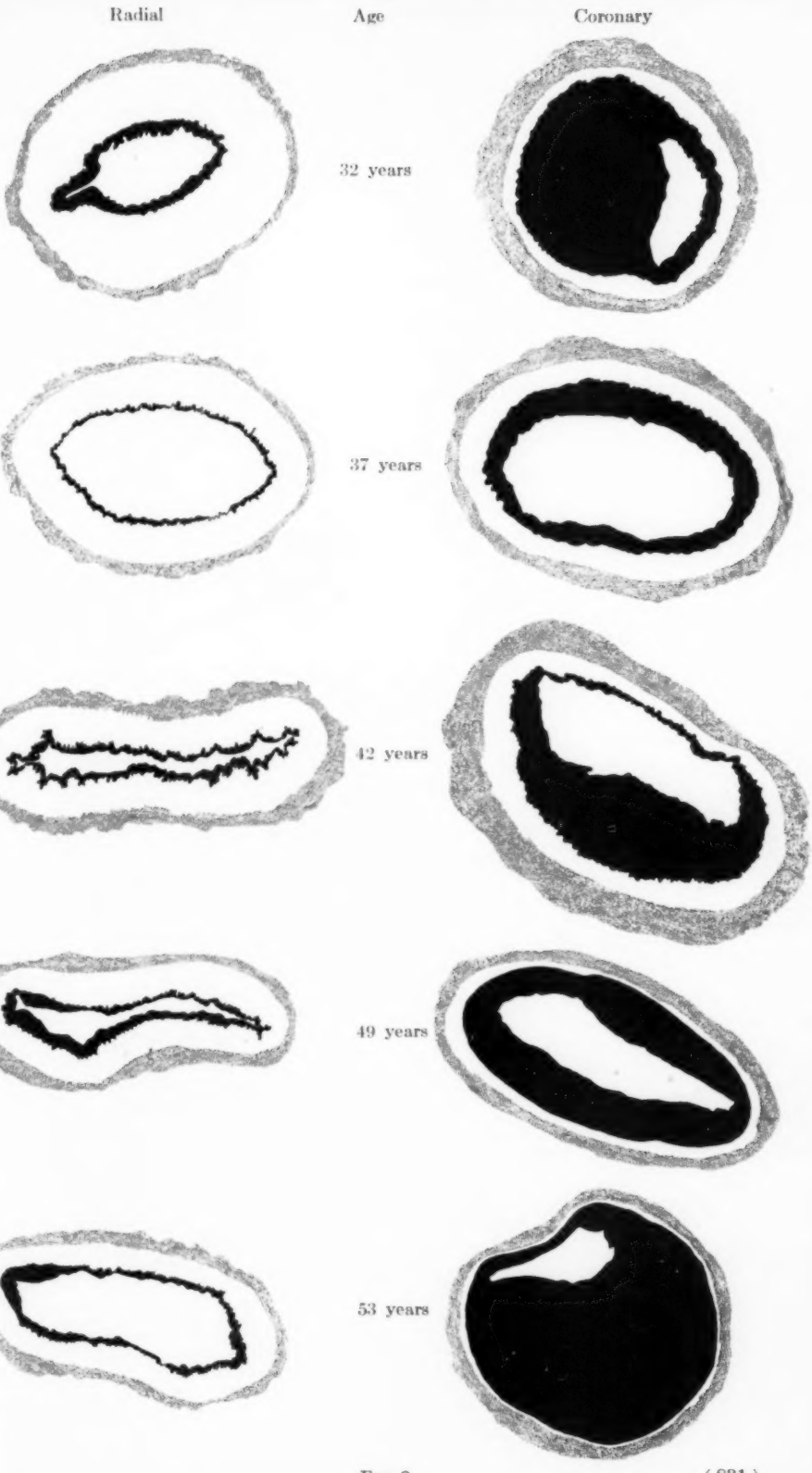
Radial
Age
Coronary
32 years
37 years
42 years
49 years
53 years

Fig. 3

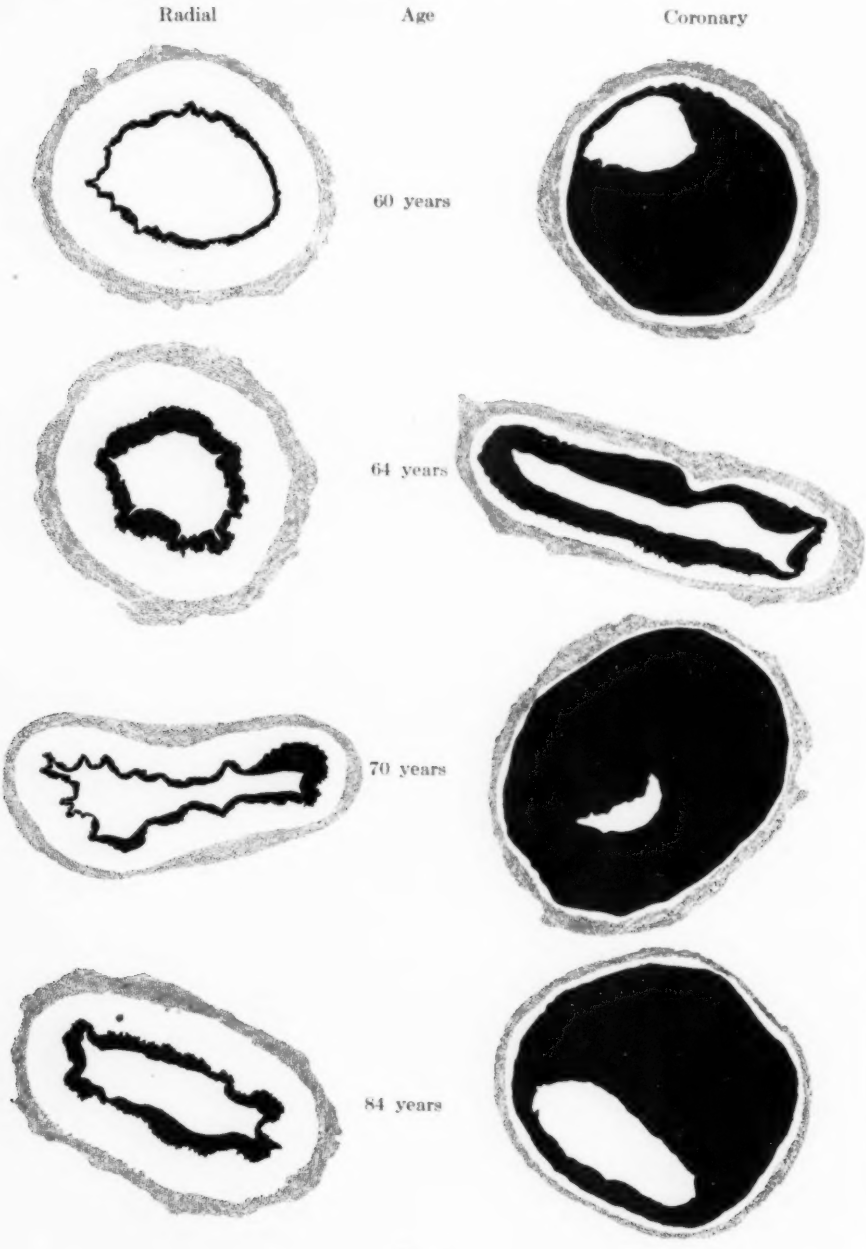

FIG. 4

seemed to us that in these cases the calcification was really medial or at least primarily so and extending into the intima and then hardly across the border. In fact, it seemed to us noteworthy that radial calcification was almost invariably medial. On the other hand, we scarcely ever saw medial calcification of the coronary. Rarely there was a very slight degree of it, but not at all of the Mönckeberg type, while intimal calcification was, of course, extremely common in the atherosclerotic regions in the coronaries. This localizing tendency in Mönckeberg's sclerosis was well illus-

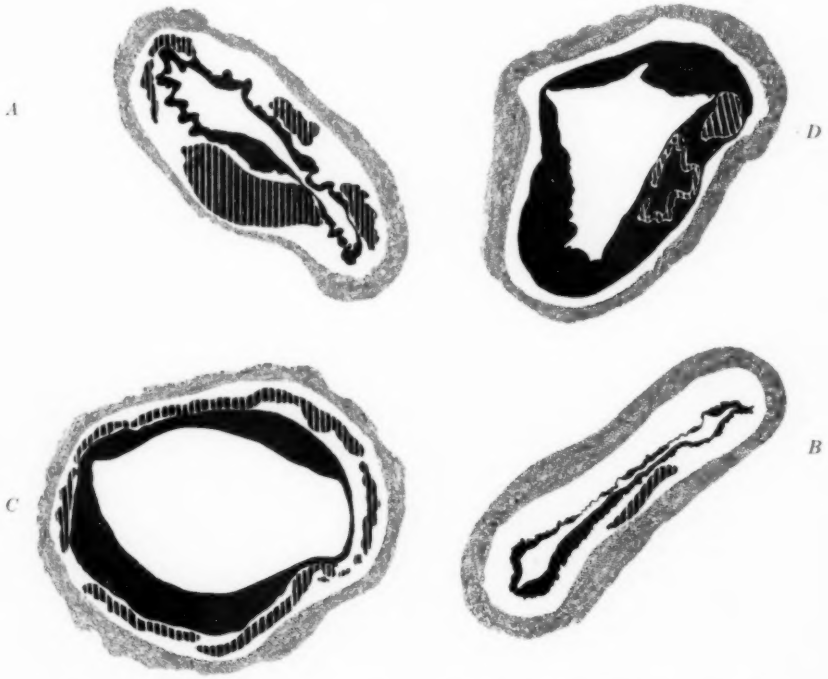

FIG. 5.—Radial, *A;* renal, *B;* splenic, *C;* and anterior descending branch of left coronary artery, *D;* and localization of calcified areas. Intima black, media white, adventitia stippled and calcified areas barred. Case 21. Patient aged 68 years.

trated in 1 case which showed extreme medial calcification in the radial and similar change though of less degree in the renal, splenic and vertebral arteries, while the coronary from the same case presented an extreme degree of intimal calcification but no involvement of the media (Fig. 5). Similar findings were obtained in another case which showed radial, renal and splenic medial calcification and coronary intimal calcification. It is curious that the coronary, structurally a muscular artery, acts, as far as atherosclerosis and calcification are concerned, like an artery of the elastic type.

There were 25 cases in which the radial artery was compared with the main renal and splenic arteries from the same patient and 7 cases in which a cerebral artery was examined as well. Of these, 80% were from subjects of 45 to 78 years. The renal, a muscular artery, is larger than the radial just as the splenic, also a muscular artery, is larger than the renal. In many instances, one artery would show decided change and the others little; or two might show change and a third but little. The changes were mostly intimal in all, but of unpredictable degrees. On the whole, we found renal changes less than radial and splenic changes more than radial. The ratio of intima to media in the renal vessel after 50 was often 1 to 5 up to 1 to 8, while the radials for the same period showed a ratio of 1 to 2 up to 1 to 5. The splenic artery noted for its tortuosity was expected to show great changes but single sections, though taken from supposed favorable sites, showed not infrequently surprisingly little change, often not more than the radial and at times less. The splenic ratio was about like the renal. The splenic, however, and occasionally the renal showed marked eccentric atherosclerotic plaques sometimes with calcification. These thickened the wall decidedly and altered the ratio locally to 5 or 10 to 1. Such a finding is almost unknown in the radial. There were 2 such plaques in 25 renal arteries and 5 in 25 splenic arteries. On the other hand, we found a renal artery from a man of 77 like that of a child of 10 with an almost perfect internal elastica. The media of the renal and splenic arteries showed, compared with the radial, an apparent diminution of muscle fibers in later life with the appearance of hyalin or bluish areas suggestive of mucin. This is seen to some extent, but much less, in the radial of older people. In examining the cerebral vessels, the normal thickness of the internal elastica and the thinness of the muscular layer was kept in mind. We examined 9 vessels in 7 cases, 2 vertebrals, 5 basilars, 1 middle cerebral and 1 internal carotid. The changes were a little more marked than in the radial. They are predominantly intimal. The media is so thin that the ratio is not so significant as in the radial or coronary. The intimal-medial ratio of thickness varied early and in milder changes from 1 to 2 to 1 to 4 but shifted to 2 to 1 to 4 to 1. Atherosclerotic intimal plaques are apparently common here and we found 2 in the 7 cases with marked eccentric thickening. In another case (Fig. 6) in which there was basilar thrombosis there was a very thick calcified plaque and a similar one in the vertebral artery while the radial showed only moderate change of the physiologic type. The intimal-medial ratio of the basilar in this was 10 to 1 as against a 1 to 4 in the radial. The coronary changes of the same case were marked and atherosclerotic but not extreme.

The distribution of calcification in this group of 25 cases was of some interest. As has been already noted, when the radial calci-

fication was medial (the Mönckeberg type), calcification, if found elsewhere as in the renal, splenic or cerebral vessels, showed the same localization while coronary calcification, if present, was almost invariably intimal. Of course, calcification either medial or intimal was not necessarily found in the other vessels when present in the radial or *vice versa*. This might be due in part to the fact we did not make multiple sections of each vessel. Whether or not there was found Mönckeberg sclerosis, the presence of an atherosclerotic sclerotic plaque presented an invitation for lime deposits and such

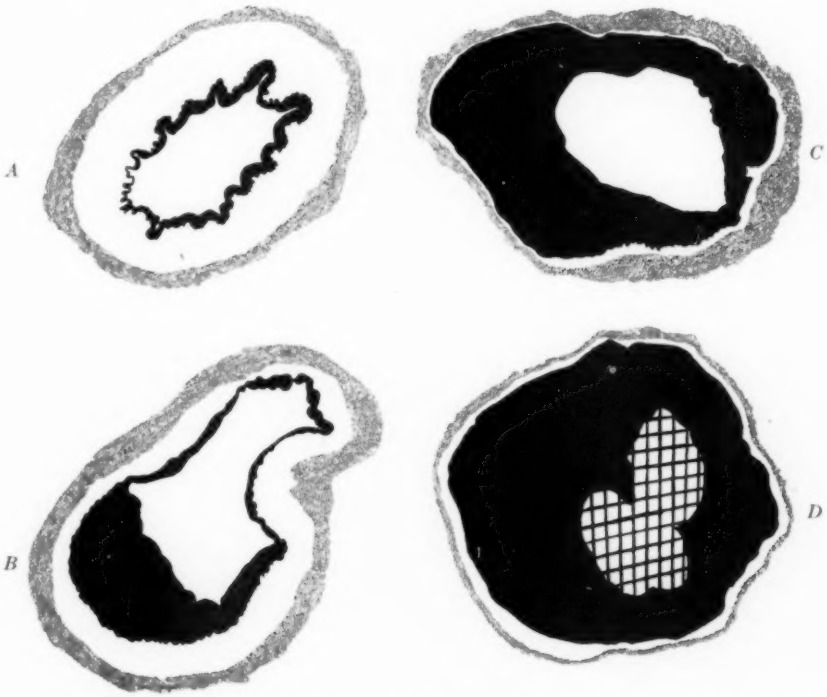

FIG. 6.—Showing variations in intimal thickening and sclerosis in radial, *A;* anterior descending branch of left coronary, *B;* left vertebral, *C;* and basilar arteries, *D*. Intima black, media white, adventitia stippled, thrombus in basilar cross-hatched. Case 19. Patient aged 60 years.

an intimal change seemed entirely independent of the medial condition. In these 25 cases we found 4 examples of radial calcification (all medial); 3 renal (1 intimal and 2 medial), 7 splenic (3 intimal and 4 medial), 2 cerebral (both medial), and 12 coronary (all intimal). These figures are somewhat of a commentary on the type of arteriosclerosis found in such vessels.

Though our material was rather meager, the vessels were scrutinized with respect to the relation of certain infections or other con-

ditions to arteriosclerotic changes. McCallum[12] finds little evidence that infections play a great part in the pathogenesis of arteriosclerosis but notes that there seems to be a definite association of arteriosclerosis with such diseases as diabetes, arteriosclerotic nephritis and cholelithiasis. Four of our cases of rheumatic infection showed no more radial or coronary change than found in many other conditions. Two of 4 cases were examples of rheumatic pancarditis in boys of 10 and 11. The boy of 11 had a heart weighing 450 gm. but even with this marked hypertrophy there was less coronary change than usual. The other 2 cases were adults with marked degrees of rheumatic mitral and aortic disease but radial and vascular coronary changes were in no way exceptional.

There were 4 cases of diabetes, aged, respectively, 37, 47, 60 and 60. The 37-year-old case showed no more than average change for that age. The other 3 showed little radial change but very marked coronary sclerosis and 1 died of coronary disease. This last case showed thrombosis of the right coronary but all his coronary vessels showed extreme atherosclerosis. The patient, aged 47, was one of diabetes terminating with erysipelas. This case showed extreme atherosclerotic narrowing of the anterior descending branch of the left coronary artery with reduction of the lumen almost to complete closure; yet the patient gave no signs and was not suspected of coronary disease. Two of the diabetic cases, in which the renal and splenic arteries were also examined, showed in 1 case atherosclerosis of the renal and in the other atherosclerosis of the splenic with calcification of the intimal plaque.

There were 8 cases of hypertension with marked nephrosclerosis. The radial changes in these were relatively slight, certainly not a feature. On the other hand, the coronary changes were extreme in 5 out of 8. These findings were more significant in 4 of the cases in which the ages were respectively 16, 22, 24 and 25 and, therefore, at a period in which the age factor or general atherosclerotic development could not be invoked to explain the sclerosis. In patients of 16 and 22, the ratio of intima to media was as high as 10 to 1 and the patient at 24 shows in the illustration (Fig. 7) the striking contrast between radial and the various coronaries. In 8 cases of hypertension with only slight or moderate renal findings, the radial changes were slight to moderate, the latter usually in late age period while the coronaries in 4 out of 8 exhibited extreme sclerosis, though the age factor here had to be considered. There were 6 cases with the clinical diagnosis of coronary thrombosis. Five of these showed extreme coronary atherosclerosis and thrombosis; but 1, aged 46, showed coronary thrombosis with very little arteriosclerosis of the coronary, though there was Mönckeberg's sclerosis of the radial. In the other 5 cases the radial showed no significant change except one which showed medial calcification.

There were a number of cases, at least 11, in which there was ex-

treme coronary disease without the clinical diagnosis or suspicion of coronary involvement. A number of these were examples of hypertension with or without nephrosclerosis and 6 died of cerebral hemorrhage. Two cases showed this extreme coronary arteriosclerosis with

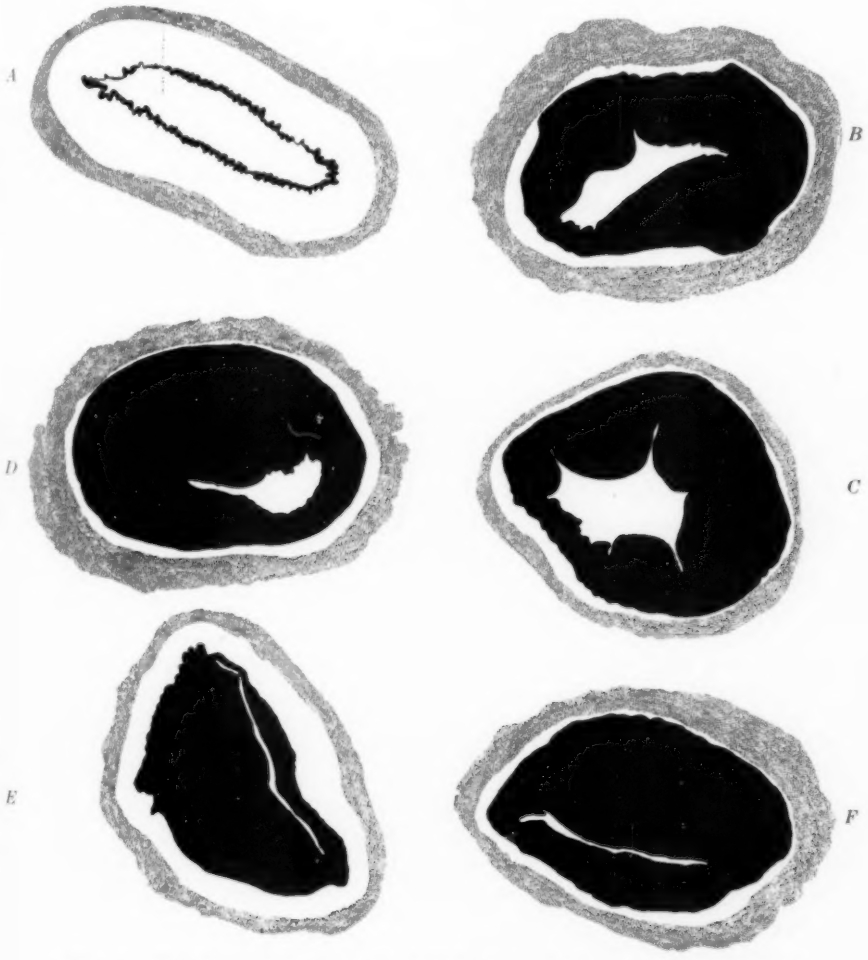

FIG. 7.—Showing variations in intimal thickening and sclerosis in radial, *A;* right circumflex, *B;* left circumflex, *C;* anterior descending branch left coronary, *D;* branch of anterior descending artery, *E;* posterior descending branch of right coronary, *F.* Intima black, media white, adventitia stippled. Case 82, patient aged 24 years.

almost complete closure of the vessels but had no kidney or heart disease or hypertension. One, aged 32, already noted, died of acute leukemia; another, aged 53, died of cancer of the rectum. These 2 patients had only the very slightest radial alteration. Two cases

of toxic goiter, one 44 and one 46, showed moderate changes in the radial with an intimal-media ratio of 1 to 3, while the coronary vessels were only slightly altered and decidedly under the average for the age. Syphilis though present in a number of cases was so involved with other diseases and conditions that it could not satisfactorily be correlated with vascular change in the radials or coronaries.

Summary. There is here presented a study of age period and arteriosclerotic changes in the radial artery in which a comparison was made between the coronary and radial vessels in the same patient in a series of 86 cases. As the changes in both are predominantly intimal, a rough but satisfactory index of change was found in the ratio of intimal to medial thickness in the two vessels. The coronary intimal-medial ratio rose rapidly from 1 to 6 or 8 to 1 to 3, 1 to 2 and 1 to 1 until in the third and fourth decades the intima equaled and not infrequently exceeded the media in thickness. After 45 years, and especially in the sixties, the addition of atherosclerotic changes raised the intimal-medial ratio still further to readings from 6 to 1 to 10 to 1. On the other hand, the radial intimal-medial ratio rose slowly to reach a maximum between 45 and 65 years, a maximum, however, which is minimal compared to coronary alterations and in which the intimal-medial ratios seldom ever go above 1 to 1 and are usually 1 to 3 or 4. This is due to the slight degree of so-called intimal physiologic thickening, compared to the great degree that obtains in the coronaries, plus the fact that augmentation of intimal thickening by atherosclerotic plaques is practically missing in the radial while it is routinely found in the coronaries after 50 years. Thus the thickest radial, found say at 65 years, has no more change than that seen physiologically in the coronary vessels at about 20 years. This inequality of age transitions is well illustrated in Figs. 1, 2, 3 and 4.

A further comparison of radials with splenic and renal arteries in 25 cases and cerebral vessels in 7 cases showed that in many instances the physiologic intimal thickening was only a little more marked than in the radial, but that these other vessels were subject at times to marked atherosclerotic developments notably absent in the radial.

Mönckeberg's medial sclerosis was present in 10% of our radials but was not found in any of the coronaries, though intimal calcification of these vessels was very common. Medial calcification, however, was found in corresponding splenic, renal and cerebral vessels along with intimal calcification of the coronaries. The Mönckeberg type of sclerosis seemed entirely independent of and unrelated to the presence or absence of atherosclerosis, except that they are both commonly found after 50 years.

Scrutinized as to the relation of certain diseases to arteriosclerotic change, it was found in the small series available that cases of diabetes and malignant and benign hypertension showed marked or extreme coronary sclerosis, while the corresponding radial was little affected. Six cases of clinical coronary disease with typic lesions showed little radial change, except one which presented Mönckeberg's sclerosis. Advanced coronary sclerosis was also unexpectedly encountered in a number of cases in which the preceding history and disease seemed entirely unrelated to such vascular change. Such cases were not suspected during life of coronary disease; certainly the radial artery gave no information.

Conclusions. The present study suggests: 1. That both age period changes and arteriosclerotic changes are maximal in the coronary arteries and minimal in the radial arteries and more or less intermediate in other vessels, such as the cerebral, splenic and renal arteries.

2. That atherosclerosis in the radial is such a rarity as to be negligible.

3. That the anatomic condition of the radial artery has no bearing on visceral sclerosis.

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THE RELATION OF CORONARY SCLEROSIS TO SYMPTOMS AND ITS DISTRIBUTION IN 242 FATAL CASES.*

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Much has been written on the subject of coronary disease, particularly in the last two decades, and some excellent reviews have been published recently. Yet comparatively little is available for a correlation of coronary arteriosclerosis and the clinical signs and symptoms. This paper is an attempt to correlate the pathological findings with the clinical picture in 242 fatal cases.

Material. Part of the material was obtained from those autopsy protocols of the University Hospital from 1926 to 1933 of which slides were accessible for study of the coronary arteries. Only those mentioning sclerotic coronaries, macroscopically or microscopically, were selected. Of 207 cases assembled, 15 were later rejected because of incompleteness, leaving 192 cases for study. Of the slides from the 192 cases, 99 showed one or more of the main subepicardial branches of the coronary arteries, while the remaining 93 showed only secondary subepicardial or intramyocardial branches. This constituted Series 1. To supplement this material a group of 50 current autopsies were more extensively studied: Series 2. Cases were selected only where sclerosis of the coronary arteries was present grossly and sections were taken of the six main superficial branches, 9 cases coming from the University Hospital and 41 from the Philadelphia General Hospital. Sections were made also of the kidney, liver, spleen, adrenal and pancreas, to compare arteriosclerosis in other organs with that in the coronaries. Sections were taken from the Anterior Descending Branch, 1 to 3 cm. from its origin in the aorta; Left Circumflex, just below the tip of the auricular appendage; Left Marginal Branch, varied but usually where the artery was thickest; Right Circumflex, 2 to 3 cm. from its origin in the aorta; Right Lateral Branch, as the artery curves down to take the lateral margin of the right ventricle; the Posterior Descending, 1 to 2 cm. from the auriculoventricular groove. After microscopic examination the sclerosis of the arterial wall was classified in the following code:

1. *Mild:* intima less than ½ the thickness of the wall (Fig. 1).
2. *Moderate:* intima from ½ to as thick as the rest of the wall (Fig. 2).
3. *Marked:* intima thicker than the rest of the wall (Fig. 3).
4. *Very Marked:* intima so thick that the lumen as found in the contracted, fixed material of the microscopic section was represented by a narrow tube or mere slit (Fig. 4). (It is recognized that during life the lumen was undoubtedly much larger.)
5. *Occlusion:* occlusion with or without canalization.

Analysis of Material. *Age.* In Series 1, there was 1 case in the first decade of life, 1 in the second, 10 in the third, 18 in the fourth, 33 in the fifth, 43 in the sixth, 55 in the seventh, 29 in the eighth, and 2 in the ninth. In Series 2, there were 2 in the fourth decade,

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FIG. 1.—Photomicrograph of section of the anterior descending branch of the left coronary artery showing mild degree of sclerosis. The internal elastic membrane, limiting the media can be seen from 1 to 4 mm. from the lumen.

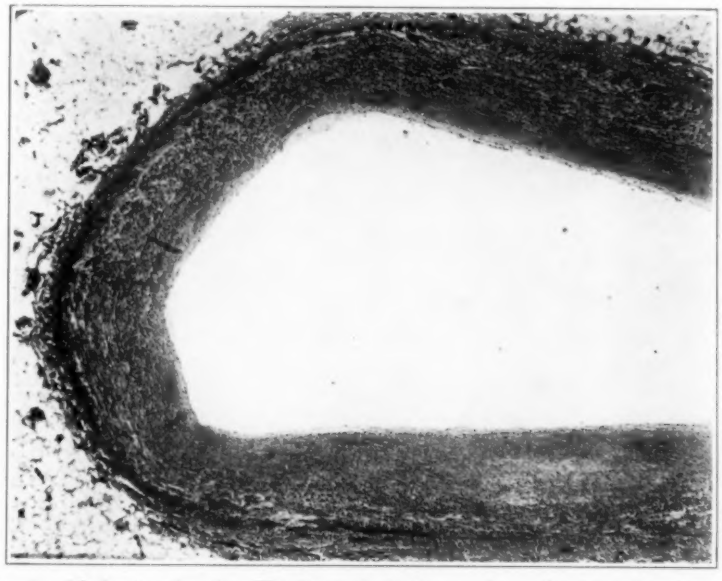

FIG. 2.—Moderate sclerosis. The internal elastic membrane lies from 7 to 10 mm. from the lumen.

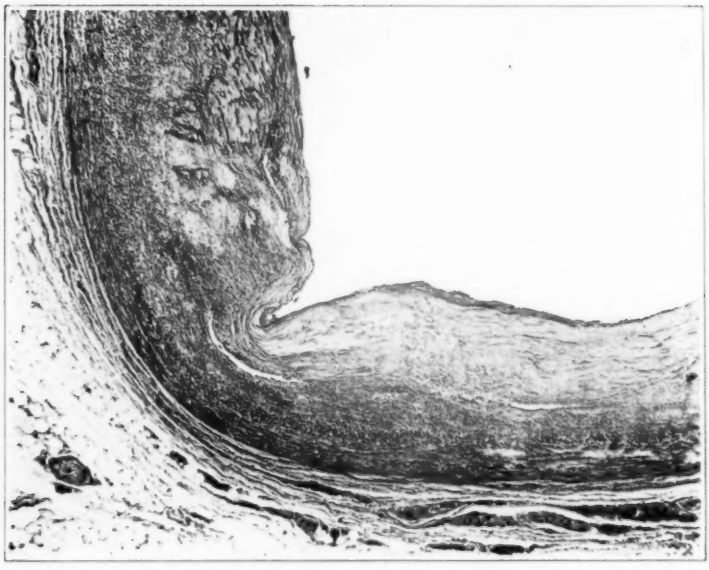

FIG. 3.—Marked sclerosis. The internal elastic membrane lies less than 1 cm. from the outer margin of the media.

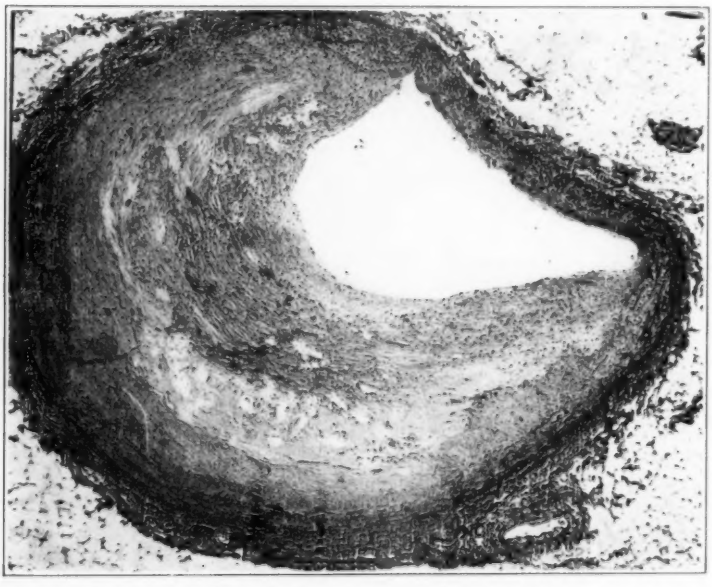

FIG. 4.—Very marked sclerosis

6 in the fifth, 15 in the sixth, 12 in the seventh, and 15 in the eighth decade. This made the combined series have 1 case in the first decade of life, 1 in the second, 10 in the third, 20 in the fourth, 39 in the fifth, 58 in the sixth, 67 in the seventh, and 44 in the eighth, and 2 in the ninth decade.

Sex. In Series 1 there were 124 males (64.6%) and 68 females; in Series 2, 32 males (64%) and 18 females. In the two series, the per cent of males to females is almost identical, the combined ratio being 156 males (64.5%) to 86 females (35.5%).

The degree of sclerosis in the 99 cases having a large branch of the coronary artery is shown in Table 1.

TABLE 1.—DEGREE OF SCLEROSIS IN THE 99 CASES EXHIBITING LARGE BRANCHES.

Degree of sclerosis	1	2	3	4	5
	Mild	Moderate	Marked	Very marked	Occlusion
Number of cases	18	20	29	26	6

Thus, of the 99 cases, 61 (61.6%), had marked sclerosis; 38 had mild to moderate; and, as will be mentioned later, 91.66% of the cases with cardiac pain were in the marked sclerotic group.

Of the 50 cases studied in greater detail, the degree of sclerosis of the six main branches of the coronary arteries and veins is tabulated in Table 2.

TABLE 2.—SCLEROSIS IN SIX MAIN BRANCHES OF CORONARY ARTERIES AND VEINS.

	Anterior descending.		Posterior descending.		Left circumflex.		Right circumflex.		Left lateral.		Right lateral.	
	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.
Mild	2	17	20	11	4	11	4	6	18	3	19	2
Moderate	4	2	9	..	2	1	11	..	9	1	13	
Marked	23	..	12	1	38	1	25	..	12	..	12	
Very marked	18	44	5	17	5	44	7	35	5	17	2	14
Occluded	3				1		3					
Not on slide		7	1			8		19	4	8	2	8
Normal		16	3	34		29		25	2	38	2	40

This showed, as one would expect, that the arteries were more sclerotic than the veins. The anterior descending branch was "very markedly" involved in the sclerotic process more than twice as many times (18 times) as the next most frequently involved (7 times) which was the right circumflex. The left circumflex was more uniformly "markedly" involved (38 times); but it was only 5 times "very markedly" involved. In a "marked" to "occluded" grouping, the order of frequency ran: anterior descending and left circumflex (each, 44 times), right circumflex (35 times), posterior descending and left lateral (each, 17 times), right lateral (14 times). The veins accompanying the different branches were often found mildly sclerosed and a few times moderately. Those accompanying the anterior descending branch were more frequently involved

(19 times) than those accompanying the lateral branch of the right coronary (2 times).

Other organs were studied to determine the degree of arteriosclerosis present and the findings tabulated in Table 3.

TABLE 3.—SCLEROSIS OF MEDIUM AND SMALL ARTERIES OF OTHER ORGANS OF THE 50 CASES OF SERIES 2.

	Kidney.		Spleen.		Liver.		Lungs.		Adrenals.		Pancreas.	
	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.
Mild	5		6		20	10	24	19	14	3	18	5
Moderate	18	14	17		11	31	13	19	16	19	17	24
Marked	18	20	16	10	5	8	2	2	2	12	3	9
Very marked	6 (24)	14	4 (20)	38	(5)	1	(3) 1		(3) 1		(5) 2	1
Normal					2		1	9			1	
Not present	3	2	5	2	11	1	9	1	17	16	9	9

This table showed that the arteriosclerosis was pretty well generalized in the 50 cases of Series 2; but that it was present in varying degrees in different organs. The kidney and spleen showed marked arteriosclerosis comparable with the heart; it must be recalled that the material was selected on the basis of the existence of coronary sclerosis.

The kidney and spleen were more severely affected than the liver as far as very marked changes were concerned. In the groups of "moderate" sclerosis, the distribution in the different organs was surprisingly uniform. This agreed with Wartman's[1] observations that the kidney and spleen were most frequently and severely involved; but it differed as far as generalized arteriosclerosis was concerned. At least, it is justifiable to say that in most cases with arteriosclerosis of the coronary vessels, arteriosclerosis was also present in vessels of other organs to a varying degree and most marked in the kidney and spleen.

Cardiac Pain. Of special interest was the question as to whether a history of cardiac pain could be correlated with the presence and intensity of coronary sclerosis. With the realization that this method would include some cases of "non-coronary" pain, it was all the more surprising that only 15.91% of Series 1 (30 out of 192 cases) showed pain of cardiac origin; and 14% (7 out of 50 cases) in Series 2 (average for the two series was 14.95%) (Table 4). In Series 1, 19 were males (1 colored); in Series 2, 5 were males. Of the females, there were 11 in Series 1 and 2 in Series 2. This made a total of 24 males and 13 females, almost 2:1.

TABLE 4.—CARDIAC PAIN ACCORDING TO DECADES IN 242 CASES.

	20–29	30–39	40–49	50–59	60–69	70–79	Total.	%
Series 1	1	2	7	7	10	3	30	15.91
Series 2			1	3	3		7	14.00

Of the 30 cases in Series 1 having cardiac pain, for 17 there were slides with large branches of the coronary arteries. Table 5 shows the degree of sclerosis in the 17 cases, together with the 7 cases of Series 2.

TABLE 5.—DEGREE OF SCLEROSIS IN CASES WITH CARDIAC PAIN.

	Mild.	Moderate.	Marked.	Very marked.	Occlusion.
Series 1		2	4	8	3
Series 2			3		4
Total		2	7	8	7

As was to be expected, most of the cases with cardiac pain (22 out of 24, or 91.7%) showed severe sclerosis; while only 2 had moderate sclerosis. No case of mild sclerosis showed pain of cardiac origin. In Series 2, 4 out of 7 cases with cardiac pain (57%) were due to occlusion.

Analysis of Signs and Symptoms. Clinical analysis of the signs and symptoms was tabulated in Tables 6, 7 and 8. Only clinical symptoms referable to the heart were recorded; and cases in which dyspnea or pain in the chest was present with pneumonia or in which the liver was found enlarged in the presence of cancer of the stomach, and so forth, were discarded.

TABLE 6.—SIGNS AND SYMPTOMS OF CARDIAC DISEASE IN BOTH SERIES (242 CASES).

					Congestive failure.				
Number cases.	Palpitation.	Precordial discomfort.	Precordial pain.	Dyspnea.	Râles or impairment at bases of lungs.	Cyanosis.	Edema of legs.	Generalized edema or anasarca.	Enlarged liver.
Series 1	11	5	30	61	36	23	27	10	24
Series 2	1	1	7	12	18	4	10	..	10
Total	12	6	37	73	54	27	37	10	34

TABLE 7.—CARDIAC PHYSICAL SIGNS AND HEMIPLEGIA.

Number cases.	Mitral systolic murmur	Presystolic murmur	Mitral double.	Aortic systolic murmur	Aortic diastolic.	Thrill.	Pulmonary systolic	Pericardial friction.	Hemiplegia.
Series 1	25	3	3	8	5	1	2	3	10
Series 2	3	1	1	4	4	1	..	2	5
Total	28	4	4	12	9	2	2	5	15

TABLE 8.—ARRHYTHMIAS.

Number cases.	Pulsus Alternans.	Gallop rhythm.	Auricular fibrillation.	Auricular flutter.	Extrasystole.	Right bundle branch block.	Left bundle branch block.
Series 1	3	1	12	1	4	1	1
Series 2			1		5		
Total	3	1	13	1	9	1	1

Thus, dyspnea was by far the most frequent symptoms complained of, the next most frequent being precordial pain. Of the physical signs, those due to congestive failure were predominant: impairment or râles at the bases of the lungs, edema of the legs, enlarged liver, cyanosis. Of the valvular signs, mitral systolic murmurs were found

twice as frequently as any other murmurs, aortic systolic coming second. Auricular fibrillation was by far the most frequent of the arrhythmias, with extrasystole next.

In an analysis of the blood pressure of Series 2, the usual single reading on first examination had to be taken as a basis. No significant results became evident. Of 30 males, 12 had systolic pressures of more than 145 mm. Hg (average, 174; extremes, 228 and 145); the diastolic average for this group was 99 mm. (extremes 146 and 70). Of the 18 men with systolic pressures under 145, the average was 115 (extremes of 140 and 80). The diastolic average of this group was 73 (range, 105 to 40). Ten of 17 females had a systolic pressure above 145 mm. Hg (average of 208; extremes, 300 and 160). Their diastolic average was 118 (extremes, 180 and 80). Females with systolic blood pressure under 145 showed: average systolic pressure, 128 (extremes 140 and 100); diastolic average, 81 (extremes 90 and 70). It is evident that the blood pressure was decidedly higher in the female group than in the male, not only as a group but individually.

Correlation of Body Weight, Surface Area and Heart Weight. Difficulty was encountered in evaluating the end results, since death in both series was due to many different causes, including cases of malignancy with accompanying loss of weight. In a study of 1000 normal hearts by Smith,[2] the weight of the normal adult heart was found to be 294 gm. for males and 250 gm. for females, with a definite correlation between the weight of the heart and that of the body. The ratio was 0.43% for males and for females, 0.4%. Heart weight increased with body weight, both absolutely and relatively; but with increase of age, the heart remained the same, provided the body weight also was stationary. Children were not included.

In the present study, data existed for 147 cases of Series 1 and 40 of Series 2. There were 95 males and 52 females in the first series, and 25 males and 15 females in the second. The average ratio of heart weight to body weight for both sexes and both series was 0.7% (being 0.7% for both males and females). Of the 120 males in the two series, the ratio of heart to body weight was normal (using the 0.43% of Smith), in only 3 cases (2.5%); below normal were 8 (6.7%), the lowest being 0.25%, while 109 (90.8% of the cases) were higher tnan 0.43%, distributed as follows:

Ratios, per cent.	Average, per cent.	Number cases.
0.44 to 0.52	0.48	25
0.53 to 0.62	0.59	21
0.63 to 0.72	0.66	17
0.73 to 0.82	0.74	20
0.83 to 0.92	0.86	8
0.93 to 1.02	0.95	11
1.03 to 1.12	1.07	4
1.13 to 1.22	1.15	2
1.23 to 1.32	1.26	1

In the two series there were 67 females whose ratio of heart weight to total weight was studied. In 6 cases, the ratio was lower than 0.4% (Smith's average normal), the lowest being 0.27%. The great majority (91%) was above 0.4%, as follows:

Ratios, per cent.	Average, per cent.	Number cases.
0.41	....	2
0.41 to 0.43	0.42	5
0.44 to 0.52	0.48	10
0.53 to 0.62	0.59	10
0.63 to 0.72	0.66	10
0.73 to 0.82	0.78	7
0.83 to 0.92	0.88	12
0.93 to 1.02	0.94	1
1.03 to 1.12	1.07	3
1.13 to 1.22	1.14	2
1.23 to 1.32	....	0
1.33 to 1.42	1.40	1

Of the 242 cases of this study, the weight of the heart was available in 227. The largest heart weighed 860 gm., the smallest, 170 (average 399). There were 149 males with an average weight of 417 gm., or 123 gm. above the normal (Smith), which is an average 42% increase; of these, the largest heart weighed 860 gm., the smallest, 270 gm. There were 78 females with an average heart weight of 387 gm., an increase of 137 gm. (55%) over normal. The largest was 800 gm., the smallest, 170 gm. The weights were grouped as follows:

Weight (grams). Males.	Average, grams.	Number cases.
Under 290	246	21
290 (normal, 294)	290	3
300 to 349	312	25
350 to 399	365	21
400 to 449	412	21
450 to 499	454	15
500 to 549	525	16
550 to 599	567	8
600 to 649	614	7
650 to 699	650	6
700 to 749	728	2
780	...	1
Over 800	828	3
Females.		
Under 250	217	10
250 (normal)	250	3
250 to 299	277	9
300 to 349	313	15
350 to 399	367	12
400 to 449	416	12
450 to 499	478	4
500 to 549	517	3
600 to 649	610	2
650 to 699	678	5
720	...	1
780	...	1
800	...	1

A study was made of the correlation of surface area, heart weight and ratio of heart weight to body weight. This was possible in the cases of 116 males and 59 females, or 175 of the cases, and is tabulated below:

Surface area in square meters. Males.	Heart weight in grams.	Ratio, heart to body weight, per cent.	Number cases.
1.30	275	0.72	4
1.40 to 1.59	349	0.71	21
1.60 to 1.79	403	0.68	44
1.80 to 1.99	468	0.65	36
2.00 to 2.19	559	0.66	8
2.30	355	0.28	1
Females.			
1.10	170	0.59	1
1.20 to 1.39	267	0.71	7
1.40 to 1.59	367	0.77	16
1.60 to 1.79	424	0.59	25
1.80 to 1.99	395	0.51	7
2.00	250	0.27	1
2.00	380	0.45	1
2.20	380	0.36	1

These findings again disclose interesting information. Of 4 males with a heart weight of 275 gm. (below normal) with a surface area of 1.3 square meters, there is still a ratio of 0.72%, higher than the Smith normal (0.43%). The same holds true for 1 female whose heart weight was 170 gm. with a surface area of 1.1 square meters and whose ratio of heart to body weight was 0.59% (normal 0.40%). There was another female with a normal heart weight of 250 gm., but with a surface area of 2 square meters whose ratio of heart weight to body weight was 0.27%, much below normal. Another whose heart weighed 380 gm., 130 above normal, but with a surface area of 2.2 square meters, gave a ratio of 0.36%. These last 2 cases recall the work of Smith and Willius,[3] and their statement, "This discrepancy may be responsible for the apparent circulatory inadequacy found in obese persons." The remaining cases showed a definite increase not only of heart weight but also an increase in ratio of heart to body weight.

Discussion. It is well known that changes in the coronary arteries start shortly after birth, consisting of splitting of the lamella elastica interna with the appearance of muscle elements between the two layers. It has also been shown[4] that these are the beginning of a series of changes that take place as the normal, healthy individual advances in years. This tendency, starting very early towards definite changes in the components of the vessel wall, makes it difficult at times to decide where the process ceases to be normal and becomes pathologic. However, since coronary arteries with normal intimal changes and with mild arteriosclerosis are comparatively free of clinical symptoms, this differentiation is not of great practical moment. This statement cannot be made too

lightly, since an apparently normal vessel may have enough sclerotic changes at the opening of the small branches to give definite symptoms.[5]

In this series, 22 of the 24 cases complaining of pain referable to the heart showed marked sclerosis and only 2 showed moderate sclerosis. None with mild sclerosis gave any history of pain. With these findings, one certainly is more inclined to believe with Sutton[6] that cardiac pain is closely related to the anoxemia of ischemia of the heart muscle. It is not clear whether this is brought about by greater rigidity of the vessel wall only or by narrowing of the lumen as well. When vessels are injected at normal pressure immediately postmortem with hardening material, it is found that even in cases of sclerosis, the lumen may not be encroached upon.[7]

The general knowledge that arteriosclerosis of the coronary arteries seems to be more prevalent in males than in females is brought out in this study, where 64.5% were males and 35.5% females. It also confirms the known fact that the anterior descending branch of the left coronary is more involved in the process than other branches. Of more unexpected interest was the finding that in this series the left circumflex was more uniformly "markedly" involved (33 times) than any other artery.

Of the clinical signs and symptoms, next to dyspnea pain was the most frequent symptom complained of. Signs of congestive heart failure predominated. Of the arrhythmias, next to auricular fibrillation, extrasystoles were the most frequent. One wonders whether they might not be produced in many cases by irritating foci, the result of arterioslerosis of small branches, such as found by Sutton and Brandes[5] on careful histologic study. Mitral systolic murmur, the most frequently found murmur, was probably due in most cases to dilatation of the mitral ring.

These clinical findings agree with those recently published by Fahr[8] in his study of hypertensive hearts. However, the similarity may be due to the fact that 90% of hypertensive hearts show decided evidence of coronary sclerosis. This brings one to the consideration of the relation of heart weight to body weight. The heart weight was relatively increased in the great majority of both males (90.8%) and females (91.3%). This increase of ratio was not due in all of the 90+% of the cases to an increase in the mass of the heart, since many were afflicted with chronic diseases, such as cancer, with an accompanying loss of weight. However, study of the actual weight of the heart in 233 cases showed that only 16.1% of the males had hearts whose weights were normal or below; and 83.9% had decidedly increased heart weights; only 16.7% of the females had normal or lower heart weight, and 83.3% were above normal. These males and females had an almost identical per cent of increased mass, so that one may conclude that in the great majority of hearts with arteriosclerotic changes in the coronaries, there is an increase in the

mass of the heart. It is probably due to an increase in the arterial pressure in the pulmonary or systemic circulation, or in both. Unfortunately, the blood pressure readings in these cases are of little value, as many were taken in stages of decompensation and do not throw light on a study of this nature.

Conclusion. Study was made of 242 consecutive cases with hearts whose coronary arteries were found postmortem to be sclerotic. There were 156 males (64.5%) and 86 females (35.5%).

History of pain of cardiac origin was given in 14.9% of the cases, of which 24 were males and 13 females; 91.7% of these were associated with marked sclerosis and 8.3% with moderate sclerosis. No cases with mild sclerosis gave a history of pain.

Dyspnea and cardiac pain were the symptoms most frequently encountered. Signs of congestive heart failure were also predominant; of the arrhythmias, auricular fibrillation was the most common, and extrasystole frequent.

The anterior descending branch of the left coronary artery was the most frequent to be "markedly" involved in the sclerotic process (18 times).

Of arteriosclerosis in other organs, the kidneys and spleen were more markedly attacked. Other organs were involved in varying degrees, showing that visceral arteriosclerosis tends to be generalized, although usually affecting the vessels of some organs more than others.

The ratio of heart weight to body weight was found to be increased in 90.8% of the males and 91.3% of the females. The average heart weight in 149 males was 417 gm. or 123 gm. (42%) above normal. Of these, 84% weighed more than normal. Of 78 females, the average weight was 387 gm., or 137 gm. (55%) above normal, 83.3% showed definite increase of heart weight.

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ADEQUATE DOSAGE IN THE SPECIFIC SERUM TREATMENT OF PNEUMOCOCCUS TYPE I PNEUMONIA.*

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With the recognition of the beneficial effects of specific antiserum in the treatment of pneumococcus Type I pneumonia and the great increase in the use of this serum since it became available in the concentrated form, it becomes desirable to attempt a definition of the effective dose of this important therapeutic agent. The obstacles which have confronted the various workers in their recent attempts to arrive at uniform standards for measuring the potency of antipneumococcic sera[1–4] have made it difficult to interpret the dosage recommended by most writers.[5–8] The realization of these difficulties has resulted in the adoption of values for the units of antibody in Types I and II antipneumococcus sera which are defined in terms of an acceptable standard serum.[4,9] The use of this standard serum coupled with the adoption of uniform methods of titration tends to fix the value of the unit within fairly narrow limits. It is desirable to know the effective dose of serum expressed in terms of such standardized units. For that purpose, the experiences with antibody treatment of the Type I cases at this hospital are here reviewed. The data with regard to the cases of pneumococcus Type II pneumonia are discussed elsewhere.[10]

Clinical Material and Serum Used. The data to be presented are based on a series of 219 cases of pneumococcus Type I pneumonia treated with serum on the medical wards (which admit only patients over 12 years) between November, 1929, and May, 1935, inclusive. The sera used were concentrated and supplied by Dr. L. D. Felton of the Department of Preventive Medicine and Hygiene, Harvard Medical School, and by Drs. B. White, E. S. Robinson, and L. A. Barnes, of the Massachusetts Department of Public Health. We are further indebted to Drs. L. D. Felton and L. A. Barnes for data regarding the titrations of the various lots of serum used, including the standards with which they were compared. These data permitted a revaluation of the dose of antibody used in each patient to make it comparable with the definition of the unit now in use, namely, the protective action of 1/300 cc. of the National Institute of Health's standard serum P11. The lots of serum used varied in

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potency from 600 to 5000 units per cc., the amounts used in each patient varying from 5 to 340 cc., or from 4000 to 1,700,000 units.

The gross death rate in all the cases receiving serum, regardless of amount or time of administration, was 18%, as compared with 39% deaths among 290 contemporaneous cases diagnosed pneumococcus Type I pneumonia during life but, for various reasons, not treated with serum (Table 1). The average amounts of serum used for each case are also shown in this table. The death rate, incidence of bacteremia, and average amounts of antibody are shown for each year in Table 2. It is apparent that these factors alone do not fully explain the differences in results observed from year to year.

TABLE 1.—DEATH RATES IN PNEUMOCOCCUS TYPE I PNEUMONIA AND AVERAGE AMOUNTS OF ANTIBODY GIVEN.

(Boston City Hospital, November, 1929, through May, 1935.)

Blood culture.	Non-serum treated.			Treated with Type I concentrated antibody.				
				Average amount antibodies.				
	Number.	Died.	Per cent.	Volume (cc.).	Units (× 1000).	Number.	Died	Per cent.
Positive . . .	100	81	81	116	202	69	25	36
Negative . . .	129	24	19	85	123	123	15	12
Not done . . .	60	8	13	74	112	27	0	0
All cases . . .	289	113	39	94	147	219	40	18

TABLE 2.—ANNUAL DEATH RATES, INCIDENCE OF BACTEREMIA, AND AVERAGE AMOUNTS OF ANTIBODY GIVEN EACH YEAR IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Year.	Non-serum treated.			Treated with concentrated antibody.					Per cent of cases with positive blood cultures.	
				Average amount of antibody per patient.						
	Number of patients.	Number died.	Per cent died.	Volume (cc.).	Units (× 1000).	Number of patients.	Number died.	Per cent died.	Non-serum treated.	Serum treated.
1929–30 . .	49	18	37	122	223	32	7	22	37	26
1930–31 . .	39	12	31	138	242	39	9	23	45	54
1931–32 . .	30	9	30	69	77	26	2	8	47	42
1932–33 . .	48	20	42	93	135	34	5	15	51	33
1933–34 . .	55	26	47	80	101	42	6	14	39	18
1934–35 . .	68	28	41	66	102	46	11	24	45	40
1929–35 . .	289	113	39	94	147	219	40	18	44	37

During the period when these patients were treated, various criteria were used to determine the initial dose of serum prescribed for each patient.[8,11,12] In general, this dose was based on volume, without due regard to antibody content, and was given in 2 to 5 intravenous injections at intervals of 2 hours. In order to minimize the occurrence of untoward reactions, a small initial injection

(usually 5 cc.) was given and this was followed by increasing amounts up to 40 or 50 cc. In patients who were not adequately improved, further doses were usually given after a lapse of 12 hours or more, the amount and frequency being gauged by the response to the earlier injections. In other patients, who seemed sufficiently improved before the time set for the final injections, the treatment was discontinued. It was usually intended to give serum only to patients in whom the first injection could be made within 96 hours of the onset of the pneumonia. A number of cases, however, were treated later in the disease due to a variety of circumstances.

In order to draw any conclusions with regard to the range of dosage which was therapeutically effective without being unduly redundant, it was necessary to analyze the effects of serum in these cases with respect to: (1) The day of illness when serum was first given; (2) the results of the blood cultures taken before treatment was begun; and (3) the efficacy of various amounts of antibody. Cases were considered therapeutic failures if the outcome was fatal or if crisis or lysis occurred later than the second day after serum treatment was begun. These therapeutic failures will be reviewed, in turn, in an attempt to determine to what extent factors, other than inadequate amounts of serum, were operating against the full efficacy of the specific antibody.

Importance of the Day of the Disease When Treatment is Begun. There are differences of opinion among physicians experienced in the serum therapy of pneumococcus Type I pneumonia with regard to the efficacy of this form of treatment when it is begun late in the disease. This lack of unanimity is found in the discussions regarding the use of both the unconcentrated[5,13] and the concentrated serums.[7,8,14] The comparatively less striking effects on the death rates and the difficulty of interpreting the clinical results when treatment is instituted late in the disease has led recent workers conducting large scale therapeutic experiments in this country[15] and in Great Britain[16] to limit this therapy, somewhat arbitrarily, to patients in whom it can be instituted within the first 4 or 5 days of the disease.

The numbers of cases treated on different days are listed in Table 3 according to the day when antibody was first given. Day 1 represents the calendar day of the initial chill or chest pain, whichever occurred first. Almost all of the cases listed as treated on the fifth day received their first injection of serum within 12 hours of the 96-hour period usually designated as the limit for treatment. It is to be kept in mind that, although the total number of cases seems adequate, the numbers become quite small when subdivided into the various categories under consideration. Any deductions made, therefore, are subject to this reservation and are necessarily based only on the general trend of the results.

TABLE 3.—INFLUENCE OF THE DURATION OF THE DISEASE AT THE TIME ANTIBODY IS FIRST ADMINISTERED ON THE OUTCOME IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Day treatment begun.	Blood culture positive.						Blood culture sterile or not done.					
	Number of cases.	Died.	Per cent died.	Recovered.* By crisis or lysis within. 2 days.	Recovered.* By crisis or lysis within. 3 or more days.	Recovered.* Empyema.	Number of cases.	Died.	Per cent died.	Recovered.* By crisis or lysis within. 2 days.	Recovered.* By crisis or lysis within. 3 or more days.	Recovered.* Empyema.
First or second	5	1	20	3	1	0	14	1	7	9	4	1
Third	16	5	31	9	2	1	34	2	6	31	1	0
Fourth	16	5	31	5	6	2	47	3	6	39	5	0
Fifth	12	3	25	5	4	6	25	2	8	18	5	0
Sixth	6	3	50	3	0	1	15	3	20	10	2	2
Seventh or later	14	8	57	2	4	0	15	4	27	7	4	2
Fifth day or earlier	49	14	29	22	13	9	120	8	7	97	15	1
Sixth day or later	20	11	55	5	4	1	30	7	23	17	6	4

* Cases with empyema are listed twice. Where the date of termination of the pneumonia was indefinite, the cases are listed as having recovered 3 or more days after treatment.

With respect to death rates, these cases divide themselves sharply into those treated on the fifth day or earlier and those treated on or after the sixth day. The death rates were essentially the same among the cases treated on each of the first 5 days of the disease. There was a sharp increase in the death rate when treatment was begun on the 6th day and a further increase among those treated still later. There was a much greater percentage of deaths among the cases with positive blood cultures, but the influence of the time factor on the death rate was similar in the bacteremic and in the non-bacteremic cases.*

The recovered cases are also of interest. In 97 (87%) of the 112 non-bacteremic patients who were treated on or before the 5th day and recovered, the disease terminated by crisis or lysis within 2 days after the first injection of serum. In fact, only 16 of these 97 cases still had fever and elevated pulse rate on the 2d day after the onset of this therapy. Among the 35 bacteremic patients who were treated on or before the 5th day and recovered, 22 (63%) recovered by crisis or lysis within the first 2 days after receiving serum; 18 of these recovered completely and 4 later developed empyema. Among the cases treated late in the disease, that is, on or after the 6th day, a smaller proportion exhibited a prompt recovery which could be reasonably attributed to serum.

The results in these cases indicate that treatment may be equally effective as a life-saving measure in cases of pneumococcus Type I

* The 27 cases in which blood cultures were not made, 6 of which were treated after the fifth day, are grouped, for the sake of convenience and brevity, together with the cases having sterile blood cultures, since the results in all these cases were very similar (see Table 1). They are here referred to as "non-bacteremic" cases.

pneumonia if begun any time within the first 5 days of the disease. It is difficult to evaluate the results of treatment begun later than the 5th day, due to the increasing number of spontaneous recoveries occurring on or after the 6th day. It would seem, however, that late treatment, particularly if begun on the 6th day, resulted in a lower death rate in bacteremic cases and brought about a more rapid termination of the disease in the recovered non-bacteremic cases.

Empyema occurred in only 1 of the 112 recovered non-bacteremic cases, in which treatment was begun on or before the 5th day, an incidence of less than 1%, whereas 4 (17%) of the 23 recovered non-bacteremic cases that were treated on the 6th day or later developed this complication. Among the 35 recovered bacteremic cases who were treated on or before the 5th day, empyema developed in 9 (26%). Up to the 5th day, there was a steady increase in the incidence of empyema proportional to the delay in treatment.

It would appear, therefore, that the administration of antibody almost eliminates the possibility of empyema developing in the non-bacteremic cases, if this treatment is begun on or before the 5th day. It tends to reduce the incidence of this complication appreciably in bacteremic cases if begun on or before the 3d day.

TABLE 4.—EFFICACY OF DIFFERENT AMOUNTS OF SPECIFIC ANTIBODY IN THE TREATMENT OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Blood culture.	Units of antibody.	Treatment begun on or before the fifth day.						Treatment begun after the fifth day.					
	Unit = 1/200 cc. of standard serum F146, or 1/300 cc. of standard serum P11.	Number of cases.	Died.	Per cent died.	Recovered.*			Number of cases.	Died.	Per cent died.	Recovered.*		
					By crisis or lysis within.		Empyema.				By crisis or lysis within.		Empyema.
					2 days.	3 or more days.					2 days.	3 or more days.	
Positive	75,000 or less	12	5	42	6	1	1	5	4	80	1	0	0
	76,000 to 150,000	16	5	31	6	5	2	4	2	50	2	0	0
	151,000 or more	21	4	19	10	7	6	11	5	45	1	5	1
Negative or not done	50,000 or less	20	0	0	16	4	0	6	3	50	3	0	1
	51,000 to 75,000	31	3	10	24	4	1						
	76,000 to 100,000	12	1	8	11	0	0	13	1	8	7	5	2
	101,000 to 150,000	35	1	3	31	3	0						
	151,000 or more	22	3	14	15	4	0	11	3	27	7	1	1

* See footnote, Table 3.

Relative Efficacy of Various Amounts of Antibody (Table 4). Among the non-bacteremic cases treated on or before the 5th day there was no correlation between the death rate and the number of units of antibody administered. Likewise, in 80% or more of the recovered cases of this group, the disease terminated by crisis or lysis within 2 days after treatment was begun regardless of

whether the dose was large or small. After the 6th day of the disease, however, the larger amounts of serum seemed to influence the disease more favorably than the smaller doses.

There was a smaller proportion of deaths among the bacteremic cases who received the larger amounts of serum. Empyema, however, was more frequent in those that recovered, when the larger doses were used. This may be accounted for, at least in part, by the fact that serum therapy was continued in such cases due to the persistence of fever and symptoms.

The distribution of cases and deaths according to the amounts of antibody given at different stages of the disease is shown roughly in Table 5. Larger doses were used more frequently in cases where the treatment was begun late in the disease. These large doses were more effective in saving life, however, in the cases where they were used early.

TABLE 5.—DISTRIBUTION OF CASES AND DEATHS ACCORDING TO THE TOTAL AMOUNT OF ANTIBODY GIVEN AND THE DAY OF ILLNESS WHEN TREATMENT WAS BEGUN.

Time treatment begun.	Blood culture positive.				Blood culture sterile or not done.			
	75,000 units or less.	76,000 to 150,000 units.	151,000 units or more.	Total.	75,000 units or less.	76,000 to 150,000 units.	151,000 units or more.	Total.
Third day or before	2* / 5	2 / 9	2 / 7	6 / 21	1 / 20	1 / 18	1 / 10	3 / 48
Fourth or fifth day	3 / 7	3 / 7	2 / 14	8 / 28	3 / 32	1 / 28	2 / 12	6 / 72
Sixth day	4 / 5	2 / 4	5 / 11	11 / 20	3 / 6	1 / 12	3 / 12	7 / 30
Total	9 / 17	7 / 20	9 / 32	25 / 69	7 / 58	3 / 58	6 / 34	16 / 150

* The superscripts represent the number of deaths.

In order to arrive at any reasonable conclusion with regard to what is the optimum dose of antibody, it is necessary further to determine for the individual cases: (1) Whether insufficient dosage could account for the therapeutic failures; (2) whether other factors were operative which could account for the poor responses; and (3) to what extent the larger doses could be considered redundant. It may suffice to consider, in some detail, only those cases which might be considered therapeutic failures. Almost all of the cases in which crisis or lysis took place within 2 days received only the dose originally prescribed for them on the basis of volume. The larger doses used in these cases resulted from the fact that more potent lots of serum were available at the time and, therefore, such doses may have been redundant. In the cases that died after a lapse of 2 or more days and in those cases in which the crisis or lysis was delayed for more than 2 days, additional antibody was usually given, but with no regularity. In a few of the cases the

doses were regulated on the basis of the absence of agglutinins in the blood.[12] The essential features of the fatal cases and those with delayed crisis are summarized in Tables 6, 7 and 8.

Poor Responses Among Non-bacteremic Cases in Which Serum Treatment Was Begun On or Before the Fifth Day (Table 6).

There were 14 cases among the 23 of this group in which a total of 75,000 units or more of antibody was given. Four of these cases had definite complications which were diagnosed and which could adequately explain the fatal outcome or the delayed improvement, namely, hemolytic streptococcic infections of the respiratory tract in Cases 2 and 5, an infected abortion in Case 23 and cardiac failure with auricular fibrillation in Case 22. There were 2 further instances, Cases 3 and 19, in which the difficulty and irregularity with which the Type I pneumococci were found suggested that some other cause or infecting agent was operative, but was not identified. In these 2 cases it is likely that the Type I pneumococcus infection, if present before serum treatment was begun, may not have been an important factor in the latter part of the illness.

Four cases in which the larger doses were used had either an entire lung consolidated (Cases 4 and 15) or bilateral lung involvement (Cases 16 and 18) at the time that serum treatment was instituted. Together with Case 11, in which 72,000 units were given, and Cases 7 and 23, which are also mentioned in other connections, these were the only cases in the group under consideration in which such extensive involvement was noted before serum treatment. Even 120,000 units were still inadequate in such cases, as judged from the results in Cases 4, 16 and 18.

In Cases 12 and 21, the initial dose of 104,000 and 96,000 units, respectively, was followed, in each instance, by what appeared to be a crisis. On the second day following this improvement there was a recurrence of fever without respiratory distress, toxemia or appreciable elevation of the pulse rate. Additional amounts of antibody were given in these cases because the temperature rose to 101° F., and the fever subsided promptly thereafter. In the 2 remaining instances in which 75,000 units or more were used (Cases 7 and 17) this dose was spread over 2 or more days.

In the 9 remaining cases, less than 75,000 units of Type I antibody were used. Except for Case 8, in which the date of onset may be questioned, the poor response in these cases may reasonably be ascribed to insufficient dosage or to doses spread over intervals that were too long. In Case 11, already mentioned, the extent of lung involvement was an additional factor in the poor response.

It thus appears that in non-bacteremic cases in which treatment is begun on or before the 5th day of illness doses in excess of 75,000 units are necessary only when the pulmonary lesion has extended beyond the confines of one lobe at the time of the first injection. When larger amounts were used in cases with a single lobe involved, the additional antibody probably served no useful purpose. These further amounts were occasioned by the failure to observe a clinical crisis because of: (1) The presence or probable presence of other infections; (2) the occurrence of slight fever similar to that observed after spontaneous crisis; or (3) the spread of dosage over 2 or more days.

Doses of less than 75,000 units are probably adequate in many non-bacteremic cases treated early, as can be seen from Table 4. In

TABLE 6.—NON-BACTEREMIC CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA SHOWING POOR RESPONSE TO SERUM TREATMENT BEGUN ON OR BEFORE FIFTH DAY OF ILLNESS.

Case.	Age.	Lobes.	Units.	Day of disease. 2	3	4	5	6	7	8	9	10	11	Remarks.
1	27	Rl	55	O	O	..	O	L	..	..	..	E		
				25	20	10								
2	21	Ru	112	O	..	..	..	..	..	..	..	..	L	Onset after sore throat; sputum = S.H. and no Pn after 3d day; otitis media = S.H.
				112										
3	43	Rl	168	O		..	PsC	..	..	..	O	..	L	Ext. Ru; small hemoptyses; rare I in sputum; cultures unsatisfactory.
				120	48									
4	51	Lul	240	O	..	O	L							
				120		120								
5	50	Rl	230	O	O	..	D	..	..	..	..	..	..	Sputum 4th day = S.H. (no Pn).
				230										
6	21	Rl	40	..	O	..	..	..	C	..	..	..	..	Asthma and bronchitis.
					20	20								
7	57	Rml	90	..	O	..	..	O	D,O	..	..	..	..	Ext. Ll; bilateral effusion and pulmonary tuberculosis at autopsy.
					45	30		15						
8	44	Rl	54	..	O,D	..	..	..	..	..	..	..	..	Moribund; delirium tremens; history unreliable; died in 4 hours.
					54									
9	22	Ll	35	..	..	O	..	O	..	..	..	..	L	
						35								
10	46	Ll	55	..	O	..	..	O	O	O,L	..	..	..	Subcutaneous abscesses during convalescence.
						25	10	10	10					
11	26	Lul	72	..	..	O	..	..	L	..	..	..	..	Rheumatic heart disease.
						48			24					
12	40	Ll	152	..	..	O	PsC		C	..	..	..	..	Fever without symptoms on 6th day.
						104		48						
13	35	Ll	48	..	O	..	O	PsC	..	O	C 15th day			Onset with atelectasis 1 day postpartum. Ext. Lu; sterile pleural effusion.
						24	24							
14	57	Ll	57	..	..	O	..	O	..	..	D	..	..	Lung culture 7th day = I.
						17	40							
15	75	Ruml	75	..	O	..	..	L?	.	D	15th	day		
						75								
16	23	RlLl	120	..	..	O	D	..	..	..	..	..	..	Jaundice (ict. index = 25); died in 12 hours.
						120								
17	22	Ll	75	..	..	..	O	..		L				
							45	30						
18	25	RmlLl	113	..	..	O	O,O	..	..	..	..	L	..	Acute alcoholism; Ext. Ru.
							113							
19	36	Rl	834	..	O	O			O	..	O,L	..	..	Meningismus; Pn I obtained irregularly.
							273	390	75		186			
20	40	Rl	27	..	..	..	O	..	..	C				
							14	13						
21	36	Ll	144	..	..	..	..	PsC	..	C	..	..	..	No blood cultures.
							96		48					
22	76	Rl	160	..	..	..	O	D	..	..	..	..	..	Auricular fibrillation; died in 21 hours.
							120	40						
23	30	Rum	195	..	..	..	O		..	*	..	*	D	*Blood cultures: 8th day = M. tetragenus; 10th day = Staph. albus; abortion of 5-month fetus on 8th day.
							75	60	30	30				

EXPLANATION OF TABLES 6, 7 AND 8.

Lobes = Lung involved at time treatment begun: Ru = right upper lobe, Rml = right middle and lower lobes; Lul = left upper and lower lobes, etc.

Units = Total amount of antibody in thousands (unit = 1/300 cc. standard serum P11 or 1/200 cc. standard serum F146).

Day of Disease = For each case: upper line gives the result of blood cultures and the termination of disease; lower line gives amount of antibody in thousands of units. O = sterile; I = positive for pneumococcus Type I; C = crisis; L = lysis; D = died; E = empyema; PsC = pseudocrisis.

Other abbreviations: Pn = pneumococcus (type indicated by Roman numeral); S.H. = hemolytic streptococcus; P.M. = postmortem; Ext. = extension of pulmonary process; B.M.C. = Bacillus mucosus capsulatus.

many instances, however, these small total doses prove inadequate to produce a rapid and complete response, particularly when they are given over a period of 2 or more days. It seems reasonable, therefore, to deduce that a total dose of 75,000 units is adequate without being redundant if: (1) It is given within a period of a few hours; (2) the treatment is begun on or before the 5th day; (3) the blood culture is sterile before the first injection of serum; and (4) the pulmonary process has not extended contralaterally or to involve an entire lung. When the pulmonary lesion has spread, doses of 150,000 units or more may be necessary and need to be given within a short period to obtain the greatest benefit. When these conditions are fulfilled and crisis is delayed for more than 2 days, other causes should be sought to explain the persistence of fever and symptoms.

Poor Responses Among Bacteremic Cases in Which Antibody Was Given On or Before the Fifth Day (Table 7). It is reasonable to expect that the presence of bacteremia should necessitate the use of large amounts of antibody to bring about an adequate therapeutic response. It is in such patients that Cole demonstrated that the blood serum is capable of neutralizing the protective antibody in antipneumococcus serum.[17] It should be kept in mind that, for purposes of gauging dosage, the blood culture should be taken just before the first dose of antibody is given. The presence of bacteremia may be missed: (1) If one relies on the results of culture taken 1 or more days previously, as illustrated in Cases 27, 29, 31, 37 and 42; or (2) if one depends on the results of cultures taken after some injections of antibody, as in Cases 30, 31 and 45; or (3) after some non-specific injections[18] have already been given, as in Case 37. In patients with low-grade bacteremia, sterile blood cultures can be obtained for several hours after the intravenous injections of hypertonic glucose or other solutions.[19] Furthermore, the amount of antibody necessary to render the blood stream of bacteremic cases of Type I pneumonia free of pneumococci varies widely. This can be accomplished with less than 30,000 units, as in Cases 30, 31 and 34, or it may require much larger doses, as in Case 46. In some instances, repeated injections of 25,000 to 100,000 units per day, or even huge doses of over half a million units, may fail to accomplish this result, as noted in Cases 25 and 40, respectively.

Among the 27 bacteremic cases under consideration who died or failed to improve promptly after treatment with antibody, 12 received 150,000 units or more. In 7 of these, more than 1 lobe was involved, including: 4 in which the dose was spread over 2 or more days, less than 100,000 units having been given during the first day of treatment (Cases 35, 36, 45 and 47); 1 in which the presence of empyema may have obscured the beneficial effects of serum (Case 39); 1 that was complicated by the occurrence of a miscarriage (Case 41); and another (Case 37) complicated by the development of a septic parotitis. In the 5 remaining cases in which the large

amounts of antibody were used, the dose was spread over a period of 2 or more days in 2 instances (Cases 25 and 33); recovery was obscured by the presence of empyema in 1 (Case 28); and in the 4th (Case 29) there was apparently no improvement in the Type I pneumococcic infection and, in addition, there were complicating urinary and intestinal infections and a mixed infection with Friedländer's bacillus in the lungs. In Case 40, the bacteremia was uninfluenced by 915,000 units given over a period of

TABLE 7.—BACTEREMIC CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA SHOWING A POOR RESPONSE TO TREATMENT WITH SERUM BEGUN ON OR BEFORE THE FIFTH DAY OF ILLNESS.

Case	Age.	Lobes.	Units.	Day of disease.											Remarks.
				1	2	3	4	5	6	7	8	9	10	11	
24	45	Rl	112	..	I 40	.. 72	O	.	O,C						
25	44	Rl	336	..	I 24	PsC 72	I 48	96	I 48	I,I 48	D,I	..	..	..	Acute alcoholism; liver cirrhosis; Ext. RuLl.
26	50	Rml	135	..	..	I 75	.. 30	30	O,L	O	..	..	..	..	Jaundice (ict. index = 50).
27	35	Rl	147	O	..	I 60	87	O	L	..	..	..	..	..	Pregnant 5 months.
28	32	Rl	216	..	I	I 161	O,O 55	O	O	..	E				
29	74	Lu	165	O	.	I 33	.. 132	..	..	I	D	..	..	..	P.M.: pyelonephritis; colitis; B.M.C. and I from lung culture.
30	34	Rl	55	..	I	O* 35	O 20	O	..	..	O	..	..	D	*After initial dose of serum.
31	30	Rl	65	..	O	I 25	O 30	O 10	O	O,L	O	D 20th		day	B.C. = S.H. on 17th day; empyema = S.H.; P.M.: heart's blood = S.H.
32	43	RmLul	144	..	..	I 72	.. 72	D	O						
33	26	Ll	150	..	..	I 90	.. 60	D	..	..	..	..	..	..	Leukopenia (W.B.C. = 1750) before death.
34	19	Ru	60	..	..	..	I 12	O 24	.. 24	..	C				
35	27	Rum	170	..	..	..	I 75	.. 95	O	L					
36	36	Rum	186	..	..	..	I 42	.. 96	.. 48	C	..	..	..	..	Delirium tremens.
37	32	Ruml	1700	..	I	O	I 650	O,O 425	O 350	L 275	..	..	..	..	Non-specific serum, 70 cc. on 2d day; parotitis 10th day.
38	42	Rl	105	..	..	I	I,I 25	I,O 30	O 20	O 10	.. 20	L	..	E	
39	26	Rml	368	..	..	I	.. 128	O	O 48	O 48	.. 48	.. 96	L	E	Empyema I first, later S.H.
40	34	Ll	915	..	..	I	I,I,I 555	I,D 360	I	..	..	..	..	..	674 colonies per cc. before serum; P.M.: empyema, resolving and organizing pneumonia, left; early Ru.
41	30	Ruml	162	..	..	..	I 144	O,D 18	..	..	..	..	..	..	Miscarriage.
42	62	Ll	128	..	O	I	.. 96	D,O 38	..	..	..	..	..	..	Ext. Lu; B.M.C. and S.H. cultured from all lobes, and I only from Ru at P.M.
43	39	Ruml	119	..	..	I	I,D 119	..	..	..	..	..	..	..	Pn III in sputum; died 10 hours after first dose.
44	43	RlLl	96	..	..	I	.. 90	D	..	..	..	..	..	..	Died 18 hours after first dose.
45	41	Ruml	174	..	..	..	..	I,I 30	O 90	.. 54	..	L	..	..	Delirium tremens; phlebitis in 2d week.
46	24	Rl	120	..	..	..	..	I 75	I	I 15	.. 15	L 15	..	E	
47	21	Lul	158	..	..	..	..	I 90	.. 68	..	..	..	E		
48	21	Rl	55	..	..	I	..	.. 55	..	..	L D 5 2d	.. day	..	E	Empyema first I, later S.H. and Staph. aureus.
49	40	Rl	68	..	..	..	..	I 68	..	..	..	..	..	..	Acute alcoholism; liver cirrhosis.
50	55	Lu	30	..	..	..	..	I 30	D,I	..	..	..	..	..	P.M.: empyema; coronary infarct.

about 30 hours. In this case the autopsy findings indicated that the pleural and pulmonary process must have begun several days before the time alleged by the patient to have marked the onset of his pneumonia. The huge doses used in Cases 37 and 40 were due to the fact that these amounts were prescribed by volume and the lot used was especially potent, containing 5000 units of Type I antibody per cc.

The 15 remaining cases received a total of less than 150,000 units and, in most instances, this dose was spread over 2 or more days. Four of these cases, including 2 in which death occurred within 18 hours after the first dose of serum, had more than 1 lobe involved at the time treatment was begun.

It is not unreasonable to suppose that the dose, in most of these cases, was inadequate or spread over too long an interval to be of maximum benefit. It is impossible, however, to tell what part these two factors played in the development of empyema or the occurrence of superinfections. The fact that these complications are less common when adequate amounts of antibody are given during the first 3 days of the disease suggests that they might be avoided, at least in some instances, by the introduction of a large amount of antibody within a few hours.

From the observations in these cases it seems reasonable to deduce that, in bacteremic cases, a dose of 150,000 units is usually sufficient to bring about an adequate therapeutic result if: (1) Treatment is begun on or before the 5th day; (2) the entire amount is given within about 24 hours; and (3) the pulmonary lesion has not extended beyond the confines of a single lobe at the time when this treatment is begun. More antibody is probably necessary if 2 or more lobes are involved; the exact amount remains undetermined but is probably not far in excess of 200,000 or 250,000 units. It is not unlikely that some cases of empyema and, perhaps, even some instances of superinfection with other organisms might be avoided if antibody is given in this manner.

Poor Responses Among Cases in Which Treatment With Antibody Was Begun After the Fifth Day (Table 8). Of the 50 cases treated on or after the 6th day, 28 (56%) either terminated fatally or failed to improve until 3 or more days after antibody treatment was begun. This is almost twice the frequency with which poor responses were encountered among the cases treated earlier in the disease (50 of 169 cases—30%). This discrepancy occurred in spite of the fact that larger doses of antibody were used more frequently (Table 5) and the average number of units used was 41% more among the cases treated after the fifth day than among those treated earlier (Table 9).

The interpretation of the results of therapy begun on the 6th day or later is difficult because spontaneous recoveries occur with increasing frequency after the 6th day. Among cases treated this late in the disease, some are likely to be *in extremis* and could hardly be expected to benefit from the antibody. In the present series, this occurred 4 times (Cases 53, 54, 70 and 72), and death followed within a few hours in each instance. Other

features, such as (1) massive bacterial invasions as in Cases 51 and 55, (2) mixed infections as in Cases 53, 64, 69, 70 and 78, (3) simple empyema as in Cases 66, 67 and 76, or (4) other focal pneumococcic complications, with or without empyema, as in Cases 59, 60 and 69, all tend to make the demonstration of clear-cut beneficial effects of antibody difficult if it is administered later than the fifth day. In addition to these cases, there were 7 in this series in which the dosage could be considered inadequate

TABLE 8.—CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA SHOWING POOR RESPONSE TO SERUM TREATMENT BEGUN AFTER THE FIFTH DAY.

Case.	Age.	Lobes.	Units.	Day of disease.												Remarks.
				4	5	6	7	8	9	10	11	12	13	14	15	
51	74	Rum	222	..	I*	.. 222	D	..	..	..	..	..	..	..	..	*1000 colonies per cc.
52	58	Lul	60	..	..	I 60	D	..	..	..	..	..	..	..	..	Day of onset doubtful.
53	66	Lu	48	..	..	I,D 48	..	..	..	..	..	..	..	..	..	Pn X also in sputum and blood.
54	39	RuILl	8	..	..	..	I,D 8	..	..	..	..	..	..	..	..	Rheumatic heart disease; died 6 hours after first dose
55	32	Lul	8	..	..	..	I* 8	I	D	..	..	..	..	..	..	*2200 colonies per cc.
56	21	Lul	90	O	..	..	I 90	..	..	D						
57	33	RILl	1020	..	..	O	I 230	190	O 390	O 240	O	O,D				
58	52	Ruml	765	..	..	..	I	I 165	O 255	I 84	O 96	O 60	O 54	.. 51	O,L	Massive atelectasis of right lung on 12th day—persisted 2 months.
59	37	Lul	190	..	..	..	..	I 120	.. 70	E	..	I D	(I 2 5th day) 31st day			Rib resection; Pn I meningitis 30th day.
60	13	Ll	264	..	..	..	I	.. 120	48	48	48	D	O	..	..	P.M.: interlobar empyema and meningitis (Pn I).
61	22	Rl	216	..	..	..	..	I	.. 120	O 96	..	..	C	..	..	Miscarriage.
62	41	Ll	189	..	O	..	..	..	I	I 96	O 24	I 60	O,C 9	..	..	Ext. Lu.
63	45	Ruml	140	..	O	I	..	..	..	5?	O 88	D	..	..	..	Ext. Lul.
64	43	Ruml	168	..	..	..	..	..	..	..	..	I,I 120	*D 48	..	..	*126 colonies Pn I before serum; 2700 colonies Pn III (no Pn I) 13th day; I and III from lung.
65	41	Lul	549	..	..	..	..	..	..	..	I	I	I	I 201	I 348	O, 16th and 17th day; lysis 18th day; sterile pleural effusion.
66	34	Rul	434	..	..	O 330	60	.. 44	..	..	E					
67	40	Rum	155	..	..	.. 155	..	..	..	E	..	..	..	..	..	No blood cultures.
68	43	Rm	5	..	..	O 5	..	O,D	I							
69	32	Lul	48	..	O	.. 48	D,O	..	..	..	..	..	..	..	..	P.M.: empyema (I) and pericarditis (I); Pn III (no Pn I) in Lu.
70	16	Lul	216	..	..	O 216	D	..	..	..	..	..	..	..	..	Died in 15 hours; strep. and I in Lu at P.M.
71	44	Ll	312	..	..	O	O 312	D	..	..	..	..	..	..	..	Sudden death 12 hours after apparent crisis.
72	37	?	37	..	..	..	O,D 37	..	..	..	..	..	..	..	..	Moribund; died in 4 hours.
73	45	Rul	96	..	..	..	..	.. 48	.. 48	..	L	..	..	..	..	No blood cultures.
74	24	Ruml	144	..	..	..	O	O,O 144	..	..	..	L				
75	23	Ll	100	..	..	..	..	O	.. 16	.. 60	.. 24	..	L	..	..	Ext. Lu and Rm.
76	27	Ll	144	..	..	..	..	..	O 144	..	..	..	L	..	E	
77	53	Rl	150	..	..	..	..	..	O 30	O 90	O	..	O 30	..	..	O 16th day and 20th day; died 21st day; P.M.: abscess Rl; I from Ll; heart's blood sterile.
78	43	All	534	..	..	..	..	..	O	O 262	O 134	.. 51	.. 38	.. 48	D	No Pn in sputum after 10th day; P.M.: multiple Staph. aureus abscesses (no Pn) in lungs.

even when judged by the criteria mentioned for cases treated earlier in the disease. The blood culture in these cases was positive in 3 (Cases 52, 56 and 63), sterile in 3 (Cases 68, 74 and 75) and not done in 1 (Case 73). There remain only 6 uncomplicated cases who received doses which could be considered adequate for cases treated earlier (Cases 57, 58, 61, 62, 65 and 71). The effect of the antibody in at least 3 of these, namely, Cases 58, 62 and 65, would suggest that much larger doses may be required in bacteremic cases who are treated later than the fifth day than those found to be adequate in similar cases in which treatment is begun on or before the fifth day. In 2 instances, Cases 58 and 62, bacteremia recurred after the blood stream had been temporarily sterilized. In Case 58, 420,000 units had been given before the last positive culture was obtained. The fact that in two-thirds of the cases noted in Table 8 the lesion had extended far beyond the confines of a single lobe at the time treatment was begun would also indicate the need for larger doses in the late cases.

TABLE 9.—COMPARISON OF THE INCIDENCE OF POOR THERAPEUTIC RESPONSES AMONG CASES TREATED BEFORE AND AFTER THE FIFTH DAY OF ILLNESS AND THE AVERAGE AMOUNT OF ANTIBODY USED.

Blood culture.		Cases treated on or before the fifth day.	Cases treated on or after the sixth day.
Positive	Number of cases	49	20
	Deaths or delayed crisis	27	15
	Per cent	55	75
	Average units per case (× 1000)	191	232
Negative or not done	Number of cases	120	30
	Deaths or delayed crisis	23	13
	Per cent	18	43
	Average units per case (× 1000)	109	167

If anything can be deduced from these late cases, therefore, it is the necessity for using larger doses of antibody than those which could be considered adequate in comparable cases treated before the 6th day. This seems to be true even under the most favorable conditions.

Comment. The rapid and dramatic clinical improvement following treatment with concentrated Type I antibody in cases of pneumococcus Type I pneumonia have been noted by many observers,[7,11] and the regularity with which such a response occurs has been previously reported.[8] These observations have justified the use of the clinical response to antibody as a guide to dosage and as an indication, when dosage has been adequate, of the presence of complicating factors interfering with the full efficacy of the antibody. In our experience, the commonest causes of the failure to observe this dramatic improvement within 8 to 24 hours after beginning treatment are, in the order of their frequency: (1) Errors in typing; (2) insufficient dosage according to the criteria set down, including dosage spread over too long an interval; (3) the beginning of focal pneumococcic complications; (4) mixed infections in the lungs; or (5) other complicating infections or febrile conditions; and (6) errors in estimating the time of onset of the disease or (7) the extent of the pulmonary lesion.

The following practical procedures are recommended in order to obtain the greatest benefit from antibody treatment: (1) An

attempt should be made to obtain a pneumococcus type as rapidly as possible, by all available methods, *whenever the diagnosis of pneumonia is suspected;* (2) blood cultures in suitable broth media should be made frequently; (3) when a Type I pneumococcus is reported, the date of onset of the pneumonia, that is the exact time of the initial chill or pleuritic pain, and the extent of the pulmonary lesion should be determined by a careful history and physical examination—a roentgenogram should be made, if feasible; (4) a blood culture should be made immediately before giving the first dose, *whether or not previous cultures were made;* (5) serum should be given promptly in the amounts noted in the summary; (6) these doses should be given with the customary precautions in as short an interval as is consistent with the safety and comfort of the patient. With the serums now available a dose of 75,000 units can be obtained in a total volume of 15 to 40 cc. and can be given, without untoward effects, in 2 or 3 doses at intervals of 2 hours or less. Depending on the particular lot of serum, the initial injection may be from 2 to 10 cc., the second may contain from 10 to 20 cc. and subsequent injections of 2 or 3 times the latter volumes may be given safely. If blood cultures are reported positive, the amounts mentioned should be given *regardless of any clinical improvement apparent in the patient.*

If no improvement takes place, or if the degree of improvement seems inadequate in view of the dosage used, then the following procedures may be necessary: (1) The bacteriologic status should be checked to ascertain whether the Type I pneumococcus is present. This means retyping the sputum, preferably from another specimen; (2) wherever possible, a direct culture of the sputum should be made, or other special methods used to determine the presence of mixed infections;[20] (3) further blood cultures should be made; (4) the patient should be investigated clinically for the presence of complications.

It may be of interest, in gauging dosage, that the incidence of bacteremia in our cases was found to be increased with advancing age, closely paralleling the death rate. It may, therefore, be desirable to begin treatment with large doses in patients over 40 and particularly in those over 50 years of age. The small numbers of cases preclude an adequate analysis of the influence of age, alcoholism, and other factors in addition to those already considered.

Skin tests with soluble specific substances,[21,22,23] and agglutination tests in the patients' sera by various techniques[12,24,25] may prove useful in determining the necessity for further amounts of antibody. The possibilities for the use of these aids have not yet been adequately explored. Our own limited experience warrants certain cautions in interpreting the results of these tests. A positive skin test with Type I soluble specific substance is an indication that sufficient antibody has been given, provided that this test is done 6 hours or more after the last injection of antibody. A negative

skin test, however, may be obtained in many instances when additional doses will serve to no useful purpose, namely, in the presence of complications or of mixed infections. The agglutination of Type I pneumococci by the patient's serum, either microscopically or macroscopically, is an indication of a sufficient excess of antibody only when this agglutination is marked. In certain instances minor degrees of clumping have been observed, particularly with the microscopic methods, before the required dose had been given, and even before the blood stream had been completely sterilized.

Summary and Conclusions. The results of specific therapy in a series of 219 cases of pneumococcus Type I pneumonia treated with concentrated antibody between November, 1929, and May, 1935, were reviewed in an attempt to determine the effective dose of this agent. For this purpose, the doses employed were reduced to values consistent with the definition of the unit of Type I antibody in terms of Felton's standard serum (F146 = 200 units per cc.) and the National Institute of Health's standard serum (P11 = 300 units per cc.).

The optimum dose was determined on the basis of the amount of antibody which brings about a rapid crisis in the largest percentage of cases without being unduly redundant. Due allowance was made for the influence of complicating factors which might mask the beneficial effects of the antibody.

On the basis of the observations in these cases, the following scheme of dosage seems justified for the treatment of uncomplicated cases of pneumococcus Type I pneumonia:

1. In cases in which treatment is begun on or before the 5th day of the disease *and* the blood culture taken before the first injection of serum is sterile *and* the pulmonary lesion is limited to a single lobe, a dose of 75,000 units is adequate provided that this entire amount is given within a few hours.

2. Under the same conditions, but with more extensive pulmonary involvement, 150,000 units should be given in a similar manner.

3. When treatment is begun on or before the 5th day and *the blood culture before the first injection is positive* a dose of 150,000 units is usually adequate provided that the lesion is still limited to a single lobe; but 200,000 or 250,000 units may be required if the pulmonary lesion has already spread before the treatment is begun. These total amounts of antibody may prove ineffective if their administration is spread over 2 or more days.

4. When treatment is begun after the 5th day of illness, only a small percentage of cases are likely to derive sufficient benefit from the antibody to warrant its use. In these cases, the dose should be much larger than is required in comparable cases treated earlier in the disease.

Empyema may be prevented by early and adequate specific treatment.

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THE BABIES' HOSPITAL OF PHILADELPHIA TWENTY-FIFTH ANNIVERSARY DINNER.

The Twenty-fifth Anniversary of the foundation of the Babies' Hospital of Philadelphia was celebrated on November 17, 1936, at a dinner at the Barclay Hotel. It was attended by three hundred friends of the institution, and took the form of a memorial in honor of Dr. Charles Andrew Fife, a founder and the first President of the Hospital.

CHARLES ANDREW FIFE, M.D.

Mr. Frederick A. Rakestraw, the President, introduced Mr. Howard A. Loeb as Toastmaster. Dr. John F. Sinclair, Medical Director, also a founder and one of the physicians active in the creation of the Hospital presented an historical sketch of the

modest beginnings of the institution first as a summer hospital at Wynnefield, Pa., followed by the establishing of a Country Hospital at Llanerch, Pa., providing care for sick babies, and fresh air and wholesome food for convalescent babies and children. A city branch was early established to meet the needs of the ambulatory sick, to care for well babies, and to insure a systematic check-up of the health of children discharged from the Country Hospital. This supervision, by doctors and public health nurses, is continued until they enter the public schools.

Some time later a large cottage at Beach Haven, N. J., was presented to the Babies' Hospital as a convalescent home for mothers with their children, where they might receive not only good care, but a rest from their arduous duties in their overcrowded homes.

Dr. Sinclair showed, that in a sense, the title of the institution is a misnomer, it is more than a hospital; it is a Health Unit, making itself responsible for the health of all members of the family, maintaining a prenatal clinic and an obstetrical service, providing complete periodic physical examination of all children brought to its attention and offering instructions to mothers in the care of their children. In addition there is a well-equipped hospital floor for acutely ill children who present diagnostic problems and require research and laboratory studies.

Dr. Philip Van Ingen, Director of Pediatric Service of the Roosevelt Hospital, New York, traced the changing conceptions of the care of the young, from the early emphasis on their religious training, to interest in their health, during the pre-school period. Community Health Work among children, which at first restricted itself to providing them with clean milk and medicine in the summer months, has been transformed into a consistent educational effort, coördinated with eternal vigilance throughout the year. In the early days, aside from the prevention of smallpox, little was known about preventive medicine for children, but the work has extended rapidly in all directions. Today it concerns itself with the avoidance of the extravagance of hospitalization by a system of preventive medicine, health supervision and convalescent care, infinitely less expensive and more effective.

Dr. Borden S. Veeder, Professor of Clinical Pediatrics, Washington University School of Medicine, St. Louis, Mo., paid an eloquent tribute to Dr. Fife, based on his life-long personal friendship with him, and his close association in the institution, once

familiarly known in Philadelphia as "Fife's Hospital." As a young practitioner, Dr. Fife was appalled by the terrible mortality among infants in the slums of the city during the summer months and the inadequacy of the facilities for their proper care. Gather-

HOSPITAL AND HEALTH CENTER

Seventh and DeLancey Streets

DEDICATED TO BABIES FOR THE PROMOTION OF HEALTH, THE PREVENTION OF DISEASE, THE TREATMENT OF ILLNESS, THE WELFARE OF CHILDREN FROM PRENATAL PERIOD TO SCHOOL AGE.

ing about him a group of physicians similarly minded, he took the first steps toward remedying this condition, and from then on until his death, the Babies' Hospital became a large part of his life. To this work he devoted himself and the institution became the soul and the heart of the man. His personal gentleness and

patience with sick and spoiled children and with anxious mothers made him eminently successful in his speciality. His Presidential Address before the American Pediatric Society set forth the duties, functions and obligations of the pediatrician in words which established an ideal that he himself attained so far as it is humanly possible.

The Hospital that he founded is no ordinary hospital; it transcends mere hospital care of the sick, and presents the newer and sounder conception of prevention, thereby reducing the need for hospitalization. It is largely due to his efforts and to those of his associates that the days are gone forever when one out of every five babies born to the under-privileged in Philadelphia, die in infancy.

At the conclusion of Dr. Veeder's address, a resolution was offered and adopted, to establish a permanent endowment fund for the Babies' Hospital as a memorial to Dr. Charles Andrew Fife.

BOOK REVIEWS AND NOTICES.

A Doctor's Odyssey. A Sentimental Record of Le Roy Crummer: Physician, Author, Bibliophile, Artist in Living, 1872–1934. By A. Gaylord Beaman. With a word in Memory by A. Edward Newton and Numerous Memoirs and Appreciations. Pp. 340; 21 illustrations. Baltimore: The Johns Hopkins Press, 1935. Price, $2.50.

The Doctor and the Public. A Study of the Sociology, Economics, Ethics, and Philosophy of Medicine, Based on Medical History. By James Peter Warbasse, M.D. Pp. 572; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, $5.00.

Over a biographical record frankly labeled "sentimental," as over the official biography and the charity performance, criticism must be, by tradition (perhaps unwarrantedly, since they are all up for sale), discreetly non-committal. Without violating tradition or the allied canons of good taste, the Reviewer, nevertheless, may be permitted in this instance to advise the potential reader of Mr. Beaman's book that he will find this not at all an odyssey in the classic meaning of the term, nor yet such a one of the interior life as emanated some years ago from Paris out of Dublin. Dr. Crummer's life, it would seem from this series of memoirs and appreciations, lacked the usual elements of external conflict and occasional inner incertitude, the triumph over which has constituted from ancient times the most enduring stimulus to literature and the imagination of mankind.

If this was a life deficient in the daily drama of the multitude, in its own more rarefied atmosphere it was colorful and productive. Dr. Crummer achieved in his lifetime an eviable reputation for his versatile accomplishments, not least among these being his bibliophilic studies and discoveries. Indeed, it is not unlikely that these are the achievements by which he will be best remembered in time to come—and it is not improbable that he would wish it so. For the paramount interest of his maturer years seems to have been in these studies. His attitude toward the study of medical history, it should be noted, for all his personal indulgence in the so-called amenities of book-collecting, was a fundamentally sane and irreproachable one. The study of medical history meant to him not an idle hour spent in the reading of medical biographies, but the attempt to trace the continuous stream of medical progress from its beginnings to his own day, to relate its development at a given period to the life of the people of that day. He looked upon it in other words not as a diversion, but as a proper, and even necessary occupation of the intelligent physician. It is the misfortune of this book that its subject too often is made, probably unjustly, to seem to posture gracefully, but meaninglessly, *in vacuo*. It is the wise man, as some one has or should have said, who dictates that his biography shall be written not by his friends but by his enemies.

Dr. Warbasse's book is a more virile illustration of the modern physician's growing tendency to see life (in the sociological sense) and see it whole. The first part of the book is, in respect of outward form at least, a more or less conventional history of medicine; that is, the story is told largely by means of paragraphic biographies interspersed with sections of explanatory background. Beginning with the eighteenth century, however, the emphasis comes more and more to be placed on movements and ideas, on the tracing of the increasing recognition by doctor and public of their interlocked

destinies. The final chapters of the book are devoted to an examination of the various systems of group medicine now in use. It will be no surprise to those familiar with the author's interest in consumers' coöperatives to find him a staunch advocate of the application of similar practices to medicine. The important fact is that Dr. Warbasse's arguments are so well documented—and set forth with so persuasive an enthusiasm—that it would be hard to conceive of any one, doctor or layman, not being stimulated by them to a more vigorous personal interest in the most important political question now confronting the medical profession. But the book is not the work of a brilliant and persuasive doctrinaire. The range of Dr. Warbasse's vision is nowhere better exemplified than in the last section of his book. Here, after nearly 550 pages of emphasis on the necessity for coöperative enterprise between the doctor and the public, he writes movingly of the physician as an individual. "The world envelops him; but, after all, it is the life he lives alone that counts. His real calling is the building of an individual. And that individual is himself—the physician." If history be properly subject to individual interpretation, which indeed is inevitable, this book makes a notable contribution to the contemporary histories of medicine. It is not distinguished for elegance of style or for adding measurably to our factual knowledge. Its virtue is the rather rare one of clothing the familiar and known in a new and more illuminating light; which, after all, is the most acceptable reason for rewriting ancient history.

W. McD., 2D.

PASSIVE VASCULAR EXERCISES AND THE CONSERVATIVE MANAGEMENT OF OBLITERATIVE ARTERIAL DISEASES OF THE EXTREMITIES. By LOUIS G. HERRMANN, A.B., M.D., Assistant Professor of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital, etc. With a Foreword by MONT R. REID, M.D. Pp. 288; 80 illustrations and 4 colored plates. Philadelphia: J. B. Lippincott Company, 1936. Price, $4.00.

THIS monograph presents in detail the author's views on the rationale and technique of treating peripheral vascular diseases by means of "passive vascular exercises" ("Pavæx therapy"). A historic section includes extensive quotations illustrating earlier efforts to influence blood flow to the extremities by changing environmental pressure. The physiology of peripheral blood flow, diagnostic procedures and conservative therapy in general are discussed briefly.

Diagrams and figures of the "Pavæx Unit" developed by the author are accompanied by complete instructions for its use in treating patients. Discussion of clinical results with "passive vascular exercise" therapy is limited to single examples of each of the main types of organic arterial diseases involving the extremities. The inclusion of more details concerning changes in skin temperature and other objective criteria of improvement would have added much to this section. Likewise, since several hundred patients had received during several years a total of many thousand hours of "Pavæx therapy," statistical tables on immediate results and follow-up data might well have been included. In discussing contraindications to "Pavæx therapy" the author minimizes, more than others would, the danger of spreading infection.

Written with the viewpoint of one interested in conservative treatment the book contains many excellent practical pointers on the possibilities and limitations of conservative therapy. It provides a summary of the experience of one clinic in a relatively new, but rapidly developing, field.

E. L.

ENDOCRINE TUMOURS AND OTHER ESSAYS. By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A., Senior Physician to the German Hospital, London. Pp. 207. London: H. K. Lewis & Co., Ltd., 1936. Price, 7s 6d.

THIS consists of miscellaneous discourses, in most cases modified reprints of, the author's articles in journals dealing with endocrine tumors; mutations as comes of such diseases as neoplasms and leukemia; congenital-developmental heredity diseases; treatment of constipation; bilious attacks induced by sea air; unilateral asymmetry; hypersplenism; and other subjects. I. Z.

DIE MOLEKULARPATHOLOGIE DER ENTZÜNDUNG. Ihre Bedeutung für das Krankheitsverstehen und Krankheitsheilen. Eine Einführung für Studierende und Ärzte. By PROF. DR. H. SCHADE, Direktor des Institutes für physikochemische Medizin an der Universität Kiel. Pp. 100; 20 illustrations and 18 tables. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 5.50.

THE application of the methods and principles of physical chemistry and of colloid chemistry to biologic problems has been very fruitful. The author of this little monograph on inflammation is well known for his larger work on "Physical Chemistry in Internal Medicine," and for his many excellent contributions to this subject. Inflammation plays so prominent a part in pathology that a summary of its "molecular pathology" is timely and welcome. The well known cardinal signs of inflammation are discussed in terms of physical chemistry; of changes in hydrogen-ion concentration, osmotic variations, localized temperature changes and so forth. At least a beginning is made in a field of great interest. It is to be regretted, however, that the references to the literature are confined to German publications. B. L.

LEHRBUCH DER INNEREN MEDIZIN. VOLS. 1 AND 2. Dritte Umgearbeitete und ergänzte Auflage. By H. ASSMANN, G. v. BERGMANN (mit F. S. TROEBE), H. BOHNENKAMP, R. DOERR, H. EPPINGER, E. GRAFE, FR. HILLER, G. KATSCH, P. MORAWITZ, A. SCHITTENHELM, R. SIEBECK, R. STAEHELIN, W. STEPP, H. STRAUB. Pp., Vol. 1, 934; Vol. 2, 846. Illustrations, Vol. 1, 171; Vol. 2, 153. Berlin: Julius Springer, 1936. Price: paper, Rm. 48; bound, Rm. 52.

THE third edition of this textbook, which came out 2 years after the second, has been somewhat remodeled. Lichtwitz and Thannhauser have been replaced by Assmann, Grafe and Bohnenkamp. A chapter on general hereditary pathology has been added. The general plan of the book, namely, "basing the clinical picture on scientific physiologic-pathologic knowledge, with emphasis on functional disturbances as a starting point of the study of diseases, and thorough consideration of the therapy," has been kept, however. The reader will regret not finding more of the recent studies of pneumococci and filtrable viruses. He will find that the chapter on kidney diseases (Straub) is somewhat old-fashioned, especially as far as the modern clinical methods and the modern concept of the bilateral hematogenous kidney diseases are concerned. The reader will discover also that the chapter on blood diseases (Schittenhelm) contains a number of obvious mistakes: recognition of the long since refuted theory of the origin of the blood cells from ordinary fibroblasts (v. Möllendorff), statements such as that acute hemorrhagic anemia is always hypochromic in nature and that renal anemia occurs in nephroses mainly, and a number of others. In general, it can be said, however, that this edition is as excellent as the former editions, and that it may be strongly recommended to students as well as to medical teachers. W. E.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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RECENT STUDIES ON ALCOHOL.

Alcohol is the most prevalent of all the noxious materials ingested by man. In view of its predilection for the central nervous system, a review of recent publications concerning alcohol is pertinent to this section. In spite of the prevalence and antiquity of the use of ethyl alcohol both as a beverage and a medicine, it is only recently that our knowledge of the biochemistry and pharmacology of alcohol has been developed to the point where it is comparable to that of other metabolites. Even now we are in ignorance of the intermediary steps in its metabolism in the animal body, and many other aspects of its utilization remain obscure or controversial. However, much interest in the subject has been manifest in the past decade, with the result that certain facts have been established which form a firm foundation for future research.

Alcohol Metabolism. It has been generally accepted since the fundamental work of Mellanby,[1] in 1919, that the ingested alcohol is absorbed as such from the gastro-intestinal tract, and burned by the tissues, the ultimate products being carbon dioxide and water, a relatively unimportant amount, not exceeding 10%, being excreted in the urine, sweat, and expired air. Furthermore, Mellanby showed that this metabolism of alcohol proceeded at a constant rate, irrespective of the concentration in the tissues, since his curves of blood alcohol plotted against time after a single dose were linear in form. This conception was in accord with the observations of subsequent workers, with the exception of Haggard and Greenberg,[2] who injected alcohol intravenously in dogs and found its rate of disappearance from the blood stream to be proportional to the amount present in the body at the time. Newman and Cutting[3] were unable to confirm this finding after intravenous administration in dogs and in man. They also found the same amount of alcohol

to be necessary to maintain the blood alcohol constant at widely varying levels. Thus the preponderance of evidence points to a constant rate of metabolism of alcohol for the individual.

This rate of metabolism is surprisingly resistant to modification. LeBreton[4] found that raising the metabolic rate of rats 100% by placing them in a cold room did not affect it, nor is violent muscular exercise effective. On the other hand, Widmark[5] and LeBreton[6] showed that proteins and amino acids definitely increased the speed of alcohol oxidation. The effect of insulin, dinitrophenol, and carbon dioxide-oxygen inhalation will be dealt with later in connection with therapy of acute alcoholism.

The preponderance of evidence indicates that alcohol may be considered as a food, as it is capable of replacing isodynamic amounts of other foodstuffs. LeBreton[7] feels that it possesses no specific dynamic action, and has demonstrated that in homeothermic animals it may supply as much as 50% of the basal metabolic requirements, and in poikilothermic animals at low temperatures as much as 90%. She goes so far as to advance the opinion that alcohol may be an intermediary in normal carbohydrate metabolism, a conjecture supported by the constant finding of a small amount of ethyl alcohol in normal blood. Moreover, there seems to be a fairly constant relationship between the basal metabolic rate of different species and their rate of alcohol metabolism.[8]

Mitchell[9] noted that, when equivalent amounts of alcohol and sucrose were added to the basic diet of two groups of rats, the rats receiving alcohol gained less than those receiving sucrose. On the other hand, the alcohol rats showed a smaller amount of feces, which he interpreted as an indication of superior digestion induced by alcohol.

That the rate of metabolism of alcohol is not increased by muscular exercise is an observation concurred in by Canzanelli, Guild, and Rapport,[10] LeBreton,[11] Carpenter,[12] Carpenter, Lee, and Burdett,[13] and Nyman and Palmlöv.[14] From this fact they conclude that alcohol cannot be utilized for muscular work, a deduction that does not seem wholly tenable, since alcohol has a definite and constant rate of metabolism, and the fact that this is not increased by exercise does not prove that no alcohol is utilized in muscular work.

Thus alcohol is seen to replace other foods for most physiologic purposes in approximately isodynamic amounts. That it is a good food does not necessarily follow, as its toxic action must also be considered.

Alcoholism and Deficiency Disease. Alcohol has long been credited with a toxic action on the peripheral nerves, the so-called alcoholic neuritis. Recently much doubt has been cast on the direct responsibility of alcohol for this condition, as well as for "alcoholic pellagra." Strauss[15] treated a number of cases of "alcoholic neuritis" with a high caloric, high vitamin diet, without cutting down on the amount of whiskey they were used to, with the result that the neuritis cleared up in spite of the presence of alcohol. In support of this is the work of Wechsler, Jervis, and Potts,[16] who found no pathologic changes in the nervous system of monkeys and cats habituated to large amounts of alcohol. Thus the present conception is that the neuritis is a deficiency disease, for which the alcohol is only secondarily responsible. This responsibility may be two-fold; in limiting the diet of the alcoholic, and

perhaps in destroying or preventing the absorption of the necessary food factors. Blotner[17] has shown that alcohol is effective in destroying the proteolytic activity of enzymes, lending support to this concept.

Acquired Tolerance to Alcohol. It is generally accepted that certain individuals can tolerate much larger doses of alcohol than can others without exhibiting signs of drunkenness. It is also thought that prolonged and habitual use of alcohol in large amounts is effective in engendering such a tolerance. Because of the great individual variation in non-habituated individuals to alcohol, and the practical impossibility of habituating human subjects for the purpose of experimental study, we have no unimpeachable evidence on this point based on experiments in man, so have had to rely on lower animals for our knowledge. Bogen[18] has recently reviewed the literature concerning this problem, without being able to arrive at any definite conclusion. That acquired tolerance exists seems incontrovertible but its mechanism remains obscure.

Poor absorption of alcohol by the habituated individual cannot be responsible for tolerance, since it has been found by Jungmichel,[19] Fleming and Stotz,[20,21] Bernhard and Goldberg,[22] and Newman and Card[23] that blood alcohol rises faster after ingestion in habituated individuals than in abstainers, indicating more rapid rather than less rapid absorption in these subjects.

Gettler and Freireich[24] felt that they demonstrated more rapid oxidation of alcohol in dogs after habituation than in normal controls. The length of time they waited before sacrificing their animals after giving the test dose leaves their work open to criticism; this time averaged little over an hour, during which no great amount of alcohol could possibly have been oxidized. Furthermore, Fleming and Stotz[25] and Bernhard and Goldberg[22] found no difference in rate of oxidation of alcohol in human habituates and abstainers, and Newman and Cutting[26,27] showed conclusively in dogs that the rate of alcohol metabolism was not increased by prolonged habituation.

The theory that tolerance to alcohol is a true tissue tolerance is subscribed to by Levy.[28,29] She found that the minimal anesthetic dose for habituated rats was greater than for abstainers, and that furthermore the alcohol content of the brains of habituated rats was higher than that of abstainers at the same depth of anesthesia. Newman and Card[23] found no difference in the minimal anesthetic dose for habituated and non-habituated dogs, but a definite tolerance of the habituated animals to lower concentrations of alcohol in the blood stream.

Thus, although the last word has not been said regarding the nature of tolerance to ethyl alcohol, it seems that a tissue tolerance rather than decreased absorption or more rapid oxidation is the responsible factor.

Treatment of Acute Alcoholism. There can be no doubt of the desirability of some therapeutic measure which would be effective in expediting the removal of alcohol from the body in acute alcoholic intoxication. Since, as we have seen, but a small amount of alcohol is eliminated by the various excretory systems, and the rate of oxidation of the substance is peculiarly resistant to variation, the problem is a difficult one.

Supniewski,[30] in 1926, showed that administration of a large dose of insulin to a rabbit at the same time alcohol was given subcutaneously was effective in almost doubling the rate at which the alcohol disap-

peared from the blood. Almost simultaneously, Widmark,[31] Serrianni,[32] and Newman and Cutting[33] published results showing insulin to be effective in increasing the rate of alcohol metabolism about 50% in dogs and men, when given in doses of from $\frac{1}{3}$ to 1 unit per kilogram. Subsequently, Bickel[34] has confirmed these observations. He feels that insulin is effective by lowering the blood sugar, and that if this is prevented no increase occurs. Newman and Cutting[33] obtained a similar effect with insulin-free pancreatic extract, but the fact that Carr, Schmitt, Harne, and Krantz[35] found this extract to contain enough insulin to significantly lower blood sugar makes this of doubtful significance.

Harger and Hulpieu,[36] Widmark,[37] and Newman and Cutting[38] have investigated the effect of dinitrophenol on the rate of alcohol metabolism, in the hope that this metabolic stimulant might be effective in burning alcohol. Large doses, exceeding that regarded as relatively safe in man, were effective in more than doubling the rate of fall of blood alcohol in animals. Neymark[39] found that the rate of elimination of methyl alcohol, which disappears from the body much slower than ethyl alcohol, could be increased almost five-fold by the drug. This is as would be expected, as Newman and Tainter[40] found the effect of dinitrophenol on alcohol metabolism to consist solely of an increased elimination of alcohol by the lungs. Since the normal rate of methyl alcohol metabolism is very much slower, the amount of increased elimination by the lungs in its case is more significant than in the case of ethyl alcohol. Using safe therapeutic doses in man, Newman and Cutting[33] could demonstrate no effect on the speed of alcohol metabolism.

In 1924, Hunter and Mudd[41] employed carbon dioxide-oxygen inhalation in the treatment of acute alcoholism. They followed the course of blood alcohol in one subject after a test dose both with and without the administration of the gas mixture, and from this single, apparently rather inconclusive, observation, assumed that the rate of alcohol metabolism was thus increased. In 1926, Van Wulfften Palthe,[42] arguing from the analogy of symptoms of alcoholic intoxication and oxygen deprivation, administered oxygen to intoxicated rabbits, and reported that they could thus survive ordinarily fatal doses of alcohol. However, Barach[43] was unable to confirm this observation. He did find, however, that intoxicated animals in an oxygen deficient atmosphere were improved by inhalation of oxygen, but relapsed on being returned to their former environment. Fleming and Reynolds[44] were unable to determine any effect on the rate of decline of blood alcohol after administration of either carbon dioxide or oxygen.

In 1935, Robinson and Selesnick[45] revived the use of carbon dioxide-oxygen therapy, and reported very good results in the clinical course of acute alcoholism after a half hour's inhalation. They further stated that this treatment effected an appreciable decrease in total body alcohol, a deduction to which Newman and Card[46] took exception. They showed that there was no significant decrease in total body alcohol, either in man or in dogs, after this period of inhalation. They considered the effect to be due entirely to increased elimination of alcohol through the lungs from hyperventilation, and showed that the amount of overbreathing produced by such a mixture of gases for the period of a

half hour was not sufficient to dispose of more than 1% of the alcohol present in the body. That the respiratory stimulation incidental to the administration of the gas might be very beneficial in a patient markedly depressed by alcohol was not denied. However, Selesnick[47] does not think the number of experiments sufficient for any definite conclusions. Subsequently, Butler[48] has found oxygen inhalation ineffective in protecting mice from a minimal lethal dose of alcohol, or in improving the condition or behavior of inebriated guinea pigs.

Thus it can be seen that the panacea for acute alcoholism is yet to be found. Dinitrophenol in safe doses is useless. Insulin in large doses is effective in increasing the rate of decline of the blood alcohol about 50%, which probably would not be a significant factor in saving life from the acute toxicity of alcohol, although it might be of use in expediting the "sobering up" process. Carbon dioxide-oxygen inhalation is definitely indicated when alcohol has depressed the respiratory center to a dangerous degree, but cannot be expected to eliminate any significant amount of alcohol from the body.

Chemical Diagnosis of Drunkenness. The extremely dangerous consequences of the operation of modern motor vehicles by drunken drivers has led to the development of more objective tests for inebriety than the traditional "smelling the breath." Within the past 10 years a great deal of work has been done in attempting to correlate the alcohol content of the various body fluids and the breath with the degree of intoxication.

Since the work of Nicloux,[49] in 1896, there have been many methods introduced for the determination of alcohol. Most of these are based on the oxidation of the alcohol by potassium dichromate, and the subsequent determination from the amount of dichromate used of the amount of alcohol present. Of the modifications recently introduced, that of Friedemann and Klaas[50] may be recommended for its extreme accuracy, that of Newman[51] for a fair degree of accuracy coupled with rapidity and simplicity, and that of Abels[52] for its extreme simplicity.

Alcohol determinations have been made on the breath, urine, blood, cerebrospinal fluid, saliva, sweat, and the various bodily tissues. For the determination of drunkenness, each possesses certain advantages and disadvantages. Fresh bladder urine contains approximately the same alcohol concentration as does blood plasma. It is not, however, always easy to obtain, especially without the coöperation of the subject. If it has remained in the bladder for some time, it may correspond better with the concentration of blood alcohol which prevailed several hours previously than with that at the time of examination. Gettler and Freireich[53] reported a closer correspondence between spinal fluid and brain than between spinal fluid and blood. However, Mehrtens and Newman[54] showed that during the first hour after taking alcohol the spinal fluid lagged markedly behind the blood alcohol and the clinical signs of intoxication. Furthermore, the difficulty of obtaining it makes it of little value for this work. Breath has the advantage of being easy to secure, but it has been shown that the rate and depth of breathing introduces a variable factor which may lead to large errors. Saliva is easy to obtain, but the possibility of unswallowed alcohol from recent imbibition must be borne in mind. Blood is probably the best from the standpoint of correlation with the degree of

inebriation. However, consent must be obtained for its withdrawal, as one may not be compelled to testify against oneself.

The interpretation of the values obtained is considerably more involved than is their determination. However, with the accumulation of a large amount of data certain generalizations have been made. Turner[55] states that intoxication is not noticeable when the blood alcohol is under 0.2%, and most other authorities consider 0.2 to 0.25% as the lower limit at which drunkenness may be diagnosed. If the same blood alcohol concentration resulted in the same degree of drunkenness in all individuals the problem would indeed be a simple one, but this is not the case. Individuals vary in their tolerance to the drug, this variation being both inborn and acquired. Thus, although the great majority of individuals may be so inebriated as not to be able to exercise due skill in operating an automobile when their blood alcohol is over 0.25%, certain individuals particularly tolerant to alcohol may not be so affected. As long as these exceptions exist, the chemical diagnosis of drunkenness cannot be absolute, but must be considered only as one bit of evidence among whatever others may be present to substantiate the diagnosis.

Psychopharmacology of Alcohol. The recent interest in the effects of sodium amytal in the psychoses and psychoneuroses, both for prolonged narcosis and to increase the *rapport* between physician and patient, has stimulated similar work with alcohol which may lead to a better understanding of the psychological effects of this substance.

The depressant nature of the drug was well demonstrated by Mullin, Kleitman, and Cooperman.[56] They showed that administration of 60 to 75 cc. of alcohol before retiring decreased the frequency of movements during the first half of the night. During the second half, when most of the alcohol should have undergone metabolism already, there was some increased motility.

In 1930, Perelman[57] induced light alcoholic intoxication in a group of schizophrenic patients, with resulting development of outbursts of crying and laughing. He felt, however, that he was successful in improving his contact with the patients. Sullivan, in discussion of a paper by Lindemann and Malamud,[58] reported success in establishing contact with psychotic patients by the use of alcohol. Newman[59] found that the intravenous injection of alcohol in psychoneurotics produced emotional instability but effected an improvement of contact with the examiner. In a small group of schizophrenics, however, there was a definite withdrawal from reality, with increase in already existing preoccupations, a marked contrast to the effect of sodium amytal in this condition. Kantorovich and Constantinovich[60] employed a similar procedure with catatonic patients, and reported good therapeutic results, although a perusal of the data shows a similarity in reaction of most of the cases to that report by Newman.

Thus it would seem that although alcohol is capable of effecting some psychologic change, the change is quantitative and of the nature of an intensification of pre-existing mood, in contrast to the qualitative changes reported with amytal.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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RECENT ADVANCES IN THE ENDOSCOPIC ASPECTS OF DISEASES OF THE FOOD AND AIR PASSAGES.

Endoscopy has earned an indispensable position for itself in the diagnosis and treatment of diseases of the upper food and air passages. It is no longer looked upon as a dramatic and spectacular means of removing an alien intruder in the tracheobroncheal tree or esophagus. A perusal of contemporary literature will disclose the remarkable changes that it has wrought in our methods of diagnosis and therapy of these areas. The most important recent contribution has been the use of gastroscopy for visualization of the interior of the stomach.

Gastric Disease.—While gastroscopy has been an accepted adjunct in the removal of a foreign body from the stomach, its use in the inspection of the interior of that viscus has followed the recent development of the flexible gastroscope with a lens system by Schindler and Wolf. In a discussion of diagnostic gastroscopy by means of his instrument, Schindler[1] states that it is now possible to visualize the interior of the stomach with safety and with but little discomfort to the patient. It provides a means of direct morphologic diagnosis of gastric lesions. It can reveal the presence of a gastritis and hypertrophic gastritis. It is of definite aid in the differential diagnosis between ulcer and neoplasm, and also is of aid in observing the extent of the lesion as well as its progress or response to treatment. The contraindications to gastroscopy are the presence of esophageal disease, aneurysm of the aorta and dangerous cardiac conditions. Benedict,[2] in a preliminary report upon the use of this method in 75 patients, was impressed with the ease and harmlessness of gastroscopy. He feels that it is a valuable adjunct to the roentgenography in the study of gastric disorders especially in the investigation of gastritis and in the differentiation between ulceration and new growths. The danger in gastroscopy as the Jacksons[3] point out

consists in the possibility of perforation of the esophagus during its introduction. They believe that the open tube is less dangerous, as the operator can always see a lumen ahead and stop the instrument if no lumen is visible. The Schindler instrument does not give a view of the lumen ahead and for that reason the operator must assure himself of the absence of esophageal disease by preliminary Roentgen examination or open tube esophagoscopy if necessary. They also point out that the removal of a foreign body or the performance of a biopsy require an open gastroscope rather than the Schindler instrument. They feel that every patient with gastric symptoms or hematemesis should have a diagnostic gastroscopy unless definite contraindications are present. This is especially true when a diagnosis of a gastric neurosis is contemplated in order that organic disease be excluded. Edwards[4] states that gastroscopy is a valuable adjunct in the diagnosis of gastric disease but does not displace roentgenology. He believes that more experience is necessary in the interpretation of the findings, but feels that it is the best means at our disposal in establishing a diagnosis of chronic gastritis. Benedict[5] feels that the diagnosis of chronic gastritis had rested upon an insecure foundation in the past. It was based mainly upon the presence of an indefinite symptomatology and the exclusion of organic gastric changes by means of the Roentgen ray. He emphasized that chronic gastritis is a definite disease most accurately diagnosed by gastroscopy. Jones, Benedict and Hampton[6] observed 5 cases of pernicious anemia in which careful studies of the stomach were made including Roentgen ray, biopsy, direct observation at laparotomy and by gastroscopy. They found atrophy of the mucosa to be present mainly during a relapse but was not consistent. They noted the disappearance of the atrophy upon the employment of a specific therapy. Chevallier[7] describes a non-inflammatory form of edema of the mucosa in the pyloric antrum of several cases of hypersensitivity that were studied with the gastroscope. The lesion appeared as a localized light rose-colored swelling, appearing and disappearing rapidly. It was associated with asthma, urticaria or other allergic states and was favorably influenced by desensitization. Jackson[8] expressed the opinion that the day was not far distant when gastroscopy would be routinely employed in the study of patients presenting gastric symptomatology. He stressed the important contraindications in the use of the flexible gastroscope but insisted that the instrument marked a new era in the investigation of the stomach.

Neoplasms of the Tracheobronchial Tree.—Neoplasms of the trachea are quite rare. In fact, Simpson and Moore[9] in their report of a case of primary adenocarcinoma located in the lower third of the trachea were able to find but 28 cases reported in the literature. They find that the occurrence of dyspnea in a person otherwise in good health and without evidence of intrathoracic disease is suggestive of tracheal new growth which can only be positively discovered by the aid of the bronchoscope. Guttman[10] reports a case of cylindroma or adenocystic basal-cell carcinoma originating in the trachea bringing the reported number of primary tracheal malignancies to 29. The presenting symptom in this case also was dyspnea without other evidence of intrathoracic disease and was similarly discovered by diagnostic bronchoscopy. Richards and Dietrich[11] observed a child of 8 months with dyspnea and

wheezing which was due to a primary fibrosarcoma of the trachea that was found at postmortem. Jackson's old truism that "all that wheezes is not asthma" is applicable to tracheal neoplasms.

For some reason the popular belief obtains that benign neoplasms of the bronchi are uncommon. Morlock and Pinchin,[12] in a study of 150 cases of bronchial neoplasm, found 9 (6%) to be benign. These 9 cases were reported in detail. The authors stress the fact that such benign neoplasms should be diagnosed early and removed by bronchoscopy in order to obviate the permanent damage to the lung that may follow prolonged bronchial obstruction. Benign or "carcinoid" epithelial tumors are commonly found in the large bronchi. Kernan[13] gives a detailed report of 10 cases. The bronchoscopic appearances were characteristic. The tumors were soft, at times moving with respiration. They bled readily upon being touched with the bronchoscope or biopsy forceps. Smaller growths could be removed with the biopsy forceps while larger growths necessitated the use of diathermy. Miller[14] reported a similar case in which bronchoscopy was employed to discover the cause of an upper lobe atelectasis. It was found to be due to a soft tumor that histologically showed epithelial cells in glandular arrangement and many bloodvessels. The bronchoscopic removal of the neoplasm cleared the atelectasis. An adenomatous polyp of the right main bronchus was found to be the cause of an atelectasis by Rosenblum and Klein[15] in a boy of 11, with improvement following the bronchoscopic removal. Kramer and Som,[16] in a review of 23 cases of adenoma of the bronchi, emphasize the benign nature of these neoplasms. They commonly cause hemoptysis, cough, wheezing, and show Roentgen evidence of obstruction and its consequences, namely, atelectasis, and ultimately, chronic suppuration and bronchiectasis. In all cases bronchoscopic removal is to be attempted and failing that the use of irradiation is to be considered. They find that 17 of their 23 patients were alive after an average period of observation of 4 years.

In no field of medicine has greater progress been made than in the endoscopic study of malignant growths of the lung. Bronchoscopy can justly claim credit for the remarkable advances that have been established. In fact, prior to the use of endoscopic methods our knowledge of these neoplasms was restricted to what information we obtained from autopsy material in the dead house. Lloyd,[17] in a study of 31 cases of bronchial malignancy, ranks bronchoscopy first in the methods of diagnosis, although 35% of his cases originated in the lung parenchyma which does not lend itself to endoscopic examination. He was able to obtain a satisfactory biopsy specimen in 17 of 24 cases in which bronchoscopy was performed. Moersch and Bowing[18] report a case of adenocarcinoma of the bronchus and emphasize the importance of bronchoscopic study in all cases of vague and indefinite pulmonary symptomatology no matter what the Roentgen findings may be. For it is quite apparent that only endoscopy can discover early and small lesions of the bronchi.

Hemoptysis.—One of the most common symptoms of pulmonary malignancy is hemoptysis. As a rule, this is small in amount yet Lederer[19] reports a case of fatal hemorrhage following bronchoscopy in a patient with an adenocarcinoma of the lung. Hemoptysis may be of other origin than carcinoma of the lung. Gerlinge[20] states that bron-

choscopy is indispensable in cases of hemoptysis of unknown origin, especially when there is no evidence of disease obtained by physical examination or Roentgen ray. He found bleeding may be due to dilated vessels or small neoplasms or other lesions that are insufficient to cause signs of its presence by effecting physical findings or noticeable Roentgen ray phenomena. Many cases of tracheal syphilis, tuberculosis, carcinoma, papilloma, angioma, varix and ulcer may cause hempotysis without evidencing any physical or Roentgen ray findings. Mounier-Kuhn[21] describes a case of hemoptysis due to hemorrhagic tracheitis. The tracheal mucosa in this instance was found to be deeply injected, thickened and hyperemic, with obliteration of normal tracheal landmarks.

Pulmonary Atelectasis.—Pulmonary atelectasis as a consequence of surgery, foreign body in the lung, and bronchial neoplasm is quite well recognized. However, that atelectasis may follow a tuberculous hemoptysis is not so well known. Heaton[22] reported a case in which dyspnea, physical and Roentgen findings indicated a blockage of the bronchus and atelectasis of the lower right lobe. At bronchoscopy, many blood clots, found as bronchial casts, were removed from the right bronchus with subsequent reëxpansion of the lung and relief of dyspnea. There was a recurrence of the incident some 6 weeks later with similar relief afforded by bronchoscopic removal of the clots. Chronic empyema may be caused by an unrelieved postpneumatic atelectasis with empyema, is the belief of Butler.[23] He feels that atelectasis may cause fibrosis of the lung parenchyma and chronic empyema that can only be relieved by extensive thoracoplasty. He states that atelectasis should be suspected when postpneumonic empyema fails to clear within a reasonable time and favors bronchoscopy for diagnosis and endobronchial aspiration. He reports a case in which bronchoscopy caused improvement in breathing and ultimate cure in postpneumonic empyema when palliative measures failed.

Pulmonary Suppuration.—Aspiration has always been conceded to be an important etiologic factor in pulmonary suppuration. Lowenthal[24] investigated 21 patients who had been operated upon in other fields than the upper respiratory or food passages, under general anesthesia. Immediate bronchoscopy following the termination of the operation disclosed pharyngeal secretions in the tracheobronchial tree in 76% of the patients; thus concurring in views held by many that aspiration is a most important factor in the production of postoperative pulmonary infections. He advocated frequent suction to the pharynx during anesthesia to decrease the amount of secretion available for aspiration.

Bronchoscopic therapy of lung suppuration continues to be the subject of many contributions to the literature. Looper[25] advocates endoscopic treatment of central abscesses especially if they communicate with a bronchus. He also favors endoscopy in cases of multiple lung abscess in which surgery is contraindicated. Rist and Soulas[26] stressed that the most brilliant results of endoscopic treatment of abscess were in those cases in which treatments were instituted early, *i. e.*, within the first 3 or 4 weeks after the formation of the abscess. They found that decided clinical improvement could be depended upon after 4 to 6 bronchoscopic treatments and that all but one of their patients required no more than 9. They feel that if prompt improvement is

not noted surgical intervention is to be considered. In another contribution, Soulas[27] concludes that endoscopic therapy is more successful in acute abscess than in chronic, curing 50% of the acute cases as compared to 15% of the chronic cases subjected to endoscopic therapy. Kernan[28] also stresses the importance of endoscopic treatment in early lung abscess and confesses its ineffectiveness in bronchiectasis. Pinchin and Morlock[29] are convinced that the early use of the bronchoscope aids in the resolution of the first stages of abscess formation in the period of pneumonitis. He feels that endoscopy is harmless and for that reason waiting to determine if an incipient infection will undergo spontaneous resorption is to risk the formation of an abscess that might necessitate longer treatment and possible surgery. Moore and Love[30] presented a preliminary report of their experience with the bronchoscopic application of an active polyvalent staphylococcic bacteriophage in 28 patients, 14 of whom had bronchiectasis, 10 pulmonary abscess, and 3 chronic bronchitis. By means of the bronchoscope they instilled 5 cc. of the bacteriophage into the affected bronchus that had been previously freed of secretions and any mechanical obstructions. Of 10 patients treated with a commercially obtained phage 4 showed improvement; of 18 treated with their own specially prepared phage, 17 showed improvement after but two instillations.

Dyspnea.—Barach[31] has introduced a noteworthy therapeutic agent in the treatment of dyspnea due to asthma and obstructive tracheobronchial lesions. He advocated the use of helium in a helium oxygen mixture to take the place of the conventional nitrogen-oxygen mixture. The lower specific gravity of the helium as compared to the nitrogen would give a mixture much less dense than that of air and would consequently be easier to breathe. This mixture was of marked benefit in 4 cases of asthma in which it was used. Two infants with obstructive lesions in the larynx and trachea were similarly benefited. This may prove to be a most valuable addition to our therapeutic armamentarium.

Esophageal Disease. Dysphagia.—The investigation by McGibbon[32] of 7 patients afflicted with dysphagia associated with anemia, reported in the literature as the Plummer-Vincent Syndrome, revealed the presence of organic esophageal lesions in 6. These were spasm and membrane at the esophageal introitus, stricture or web at the cricoid area, and chronic esophagitis. It is possible that the anemia is consequent to the restricted dietary due to the dysphagia.

Dysphagia due to esophageal stenosis following the ingestion of lye is well known. Other substances may cause similar catastrophy. Pitkin[33] reported a case of stricture due to the accidental administration of lactic acid. The infant was being fed a milk mixture acidified by the addition of lactic acid and was given the acid by mistaking the identity of the bottle. Dysphagia, due to stricture, appeared some 3 weeks later and required gastrostomy and retrograde dilatation. Kearney[34] reports a similar case due to the ingestion of sulphuric acid. It is obvious that more care should be exhibited in the handling of such escharotic agents. Careful labeling and identifying bottle structure should be enforced by law for all mixtures containing caustic preparations, such as paint removers, drain-pipe cleaners and the like, that are used universally today. That such legislation is effectual is proved by a survey of esophageal stricture resulting from caustic alkalies made by

Tayler.[35] He found a decrease of more than 50% in the incidence in states in which legislation has gone into effect, in spite of the enormous increase in the use of such chemicals. Dysphagia may also be due to a paraesophageal diaphragmatic hernia. Vinson and Moersch[36] report several cases associated with intermittent dysphagia and pain. They were able to discover by esophagoscopy the presence of a stricture in 2 cases and cardiospasm in a third.

Neoplasms.—While most neoplasms of the esophagus are malignant, occasionally benign growths are encountered. Such growths are usually difficult to discover and may be only found by esophagoscopy. Moersch and Broders[37] report a case of adenoma of the esophagus that caused dysphagia and epigastric burning. Roentgenologic study revealed an unusual narrowing of the esophagus which at esophagoscopy showed as a flat mass. A piece taken for biopsy was ultimately reported as an adenoma. In addition the patient was found to have a duodenal ulcer.

Carcinoma of the esophagus is well known as a clinical entity. It is unfortunate, however, that the usual picture of the disease that we are accustomed to recognize is the terminal one and therefore is of little value in aiding the patient. Our efforts must be extended in attempting to recognize the early stages of the growth. Jackson[38] believes that this lamentable inability to make an early diagnosis is in a great measure responsible for the practically 100% mortality associated with carcinoma of the esophagus. Roentgen study and esophagoscopy are, therefore, indicated in every case of disturbance of the swallowing function. Not all carcinomas of the esophagus give rise to dysphagia. Mathews and Schnabel,[39] in a clinical and pathologic study of 108 autopsies, find that some 20% of esophageal carcinomas are non-stenosing and therefore not apt to cause dysphagia. These non-stenosing growths were usually found in the lower two-thirds of the viscus. The treatment of this disorder, as a rule, is a fruitless one, although Steele[40] believes the use of endoscopic introduction of radon seeds associated with deep external irradiation may have certain possibilities.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 19, 1936

A New Graphic-Mathematical Analysis of Absorption Spectra, as Applied to Hemoglobin Derivatives.—D. L. Drabkin (Department of Physiological Chemistry, University of Pennsylvania). The absorption spectra in the visible and ultraviolet regions (from λ700 to λ200 $_{m}\mu$) of various hemoglobin derivatives—oxyhemoglobin, carboxyhemoglobin, acid and alkaline methemoglobins, cyanmethemoglobin and pyridine hemochromogen—have been subjected to analysis.

The positions of most of the maxima in the absorption curves of these hemoglobin derivatives are at equal frequency distances from each other. These positions may be expressed by $n = \frac{\nu \times 10^{-2}}{\nu_0 \times 10^{-2}}$, where n is an integer (4, 5, 6, 7, 8, 9, 10 and 11 in the spectra studied) and $\nu_0 \times 10^{-2}$, representing the fundamental frequency, is 40. Two other maxima in the green region (visible), which do not belong to the above series, are also present in all the derivatives.

The graphic-mathematical analysis indicates that the absorption curves are the additive result of individual units or bands, which may be conveniently expressed as normal frequency curves of the form $y = ke^{-\frac{(x-a)^2}{2\sigma^2}}$. The summation, Σ, of unit curves of this type

accurately reproduces the total absorption curve, which is mathematically given by $\Sigma y^n = ke - \frac{(x - [n.40])^2}{2\sigma^2}$

The analysis brings out the non-obvious, fundamental similarity in the absorption spectra of the various hemoglobin derivatives, and may lead to an understanding of certain problems in connection with the molecular structure of these substances.

Enlarged Hypophyses in Old Albino Rats.—W. H. F. Addison (Department of Anatomy, University of Pennsylvania). Greatly enlarged hypophyses have been found infrequently in old rats of both sexes in The Wistar Institute colony. The weight of the enlarged hypophyses averaged 20 times that found in other animals of the same age. Thus in a female of 1028 days, the enlarged hypophysis weighed 0.238 gm., and in a female of 961 days with an hypophysis of the usual size, the weight of the hypophysis was 0.0116 gm. In a male of 960 days, the weight of the enlarged hypophysis was 0.279 gm. and in a male of 1100 days, the weight was 0.012 gm. All the rats were of normal body size. The other ductless glands were weighed, but the weights showed nothing significant. Microscopic sections of the enlarged hypophyses show, in the pars anterior propria, the presence of numerous thin-walled blood channels, many widely distended with blood and some hemorrhagic areas. There is great increase in the gland-cell population and the cells are nearly all of the chromophobe undifferentiated type.

The Effect of Pituitrin, Water, Theophylline and Salyrgan on the Renal Blood Flow and Creatinine Clearance of Unanesthetized Rabbits and Dogs.—A. M. Walker, C. F. Schmidt, K. A. Elsom, and C. G Johnston (Laboratories of Pharmacology and Research Surgery, University of Pennsylvania). Renal blood flow was measured by an electrical thermostromuhr recently described by Schmidt and Walker; at the end of each experiment the instrument, undisturbed in its position on the renal artery, was calibrated by comparison with the method of Barcroft and Brodie. Creatinine clearances were measured by the usual technique.

Antidiuresis was produced in 20 animals by the subcutaneous injection of pituitrin. The renal blood flow and creatinine clearances remained substantially unaltered. Clearly, renal vasoconstriction was not responsible for the antidiuresis.

Water, administered by mouth to 36 animals, produced tenfold increases in urine volume. There was no consistent increase in renal blood flow as the diuresis developed and in 123 of 211 periods where urine volume changed the renal blood flow did not alter in the same direction. Creatinine clearances in dogs showed no consistent change; in rabbits they usually increased but not to a degree proportional to the diureses.

Renal blood flow was increased during the diureses produced by theophylline in 11 rabbits but the increase endured only one-third as long as the diuresis. Although the creatinine clearances usually rose, the increases were not proportional to the extent of the diureses.

During diureses produced by salyrgan in 10 dogs, the renal blood

flow showed no increase above the control level in 7 instances. The creatinine clearances were usually decreased.

It is concluded that, insofar as renal blood flow and creatinine clearances reveal glomerular function, the glomerulus plays a very subsidiary rôle in regulating urine volume. The average renal blood flow in unanesthetized rabbits was found to be 3.2 cc. per gram per minute, the average percentage of plasma filtered by the glomeruli to be 30.2.

The Relative Biological Effectiveness of Fast Neutrons and Roentgen Rays Upon Different Organisms.—R. E. ZIRKLE (Johnson Foundation, University of Pennsylvania, with collaboration of P. C. AEBERSOLD and E. R. DEMPSTER, University of California). Large numbers of two small organisms—the Drosophila egg and the wheat seedling—were irradiated with various amounts of 200 kv. Roentgen rays and of fast neutrons generated in the University of California cyclotron.

For the wheat seedling, one ionization unit of neutrons was found to be biologically equivalent to 5 units of Roentgen rays, whereas for the Drosophila egg 1 unit of neutrons was equivalent to only 2 units of Roentgen rays. Hence, in general, the biologic effectiveness of neutrons relative to Roentgen rays is greater for some cells than for others. This general fact has important practical implications, for it indicates the possibility that the effectiveness of neutrons upon tumors *in vivo*, relative to Roentgen rays, may be greater than upon normal tissues.

Correction. On page 705 of the last number (November) of this JOURNAL the Editor inserted a footnote based on erroneous information which he now wishes to correct with apology to the makers of orthoiodoxybenzoate. It is not correct that this drug contains cincophen, also the agranulocytosis patient referred to was later found to have taken fairly large doses of a drug containing amidopyrine as well.—EDITOR.

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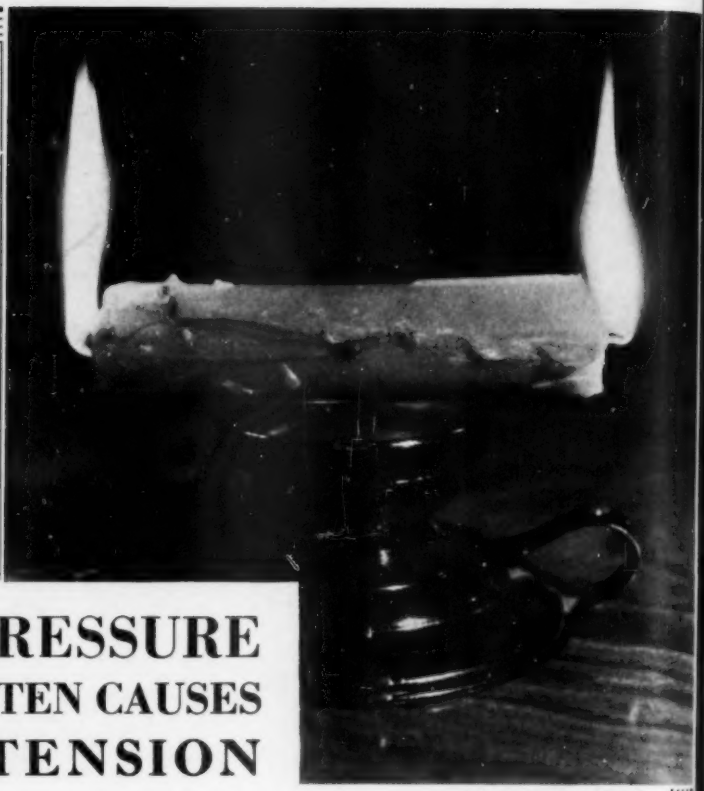

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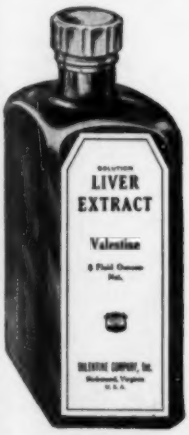

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